Document made available under the Patent Cooperation Treaty (PCT)

International application number: PCT/EP05/051086

International filing date: 10 March 2005 (10.03.2005)

Document type: Certified copy of priority document

Document details: Country/Office: EP
Number: 04101003.4
Filing date: 11 March 2004 (11.03.2004)

Date of receipt at the International Bureau: 12 April 2005 (12.04.2005)

Remark: Priority document submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b)

Europäisches Patentamt
European Patent Office
Office européen des brevets

Bescheinigung Certificate Attestation

Die angehefteten Unterlagen stimmen mit der ursprünglich eingereichten Fassung der auf dem nächsten Blatt bezeichneten europäischen Patentanmeldung überein.

The attached documents are exact copies of the European patent application described on the following page, as originally filed.

Les documents fixés à cette attestation sont conformes à la version initialement déposée de la demande de brevet européen spécifiée à la page suivante.

Patentanmeldung Nr. Patent application No. Demande de brevet n°

04101003.4

Der Präsident des Europäischen Patentamts;
Im Auftrag

For the President of the European Patent Office

Le Président de l'Office européen des brevets
p.o.

R C van Dijk

Anmeldung Nr:
Application no.: 04101003.4
Demande no:

Anmeldetag:
Date of filing: 11.03.04
Date de dépôt:

Anmelder/Applicant(s)/Demandeur(s):

ALTANA Pharma AG
Byk-Gulden-Strasse 2
78467 Konstanz
ALLEMAGNE

Bezeichnung der Erfindung/Title of the invention/Titre de l'invention:
(Falls die Bezeichnung der Erfindung nicht angegeben ist, siehe Beschreibung.
If no title is shown please refer to the description.
Si aucun titre n'est indiqué se referer à la description.)

NOVEL SULPHONYLPYRROLES

In Anspruch genommene Priorität(en) / Priority(ies) claimed /Priorité(s) revendiquée(s)
Staat/Tag/Aktenzeichen/State/Date/File no./Pays/Date/Numéro de dépôt:

Internationale Patentklassifikation/International Patent Classification/
Classification internationale des brevets:

C07D207/00

Am Anmeldetag benannte Vertragstaaten/Contracting states designated at date of filing/Etats contractants désignées lors du dépôt:

AT BE BG CH CY CZ DE DK EE ES FI FR GB GR HU IE IT LU MC NL PL PT RO SE SI SK TR LI

Novel Sulphonylpyrroles

Field of application of the invention

The invention relates to novel N-sulphonylpyrrole derivatives, which are used in the pharmaceutical industry for the production of pharmaceutical compositions.

Known technical background

Transcriptional regulation in cells is a complex biological process. One basic principle is regulation by posttranslational modification of histone proteins, namely histone proteins H2A/B, H3 and H4 forming the octameric histone core complex. These complex N-terminal modifications at lysine residues by acetylation or methylation and at serine residues by phosphorylation constitute part of the so called "histone code" (Strahl & Ellis, Nature 403, 41-45, 2000). In a simple model, acetylation of positively charged lysine residues decreases affinity to negatively charged DNA, which now becomes accessible for the entry of transcription factors.

Histone acetylation and deacetylation is catalysed by histone acetyltransferases (HATs) and histone deacetylases (HDACs). HDACs are associated with transcriptional repressor complexes, switching chromatin to a transcriptionally inactive, silent structure (Marks et al. Nature Cancer Rev 1, 194-202, 2001). The opposite holds true for HATs which are associated with transcriptional activator complexes. Three different classes of HDACs have been described so far, namely class I (HDAC 1-3, 8) with Mr = 42-55 kDa primarily located in the nucleus and sensitive towards inhibition by Trichostatin A (TSA), class II (HDAC 4-7, 9, 10) with Mr = 120-130kDa and TSA sensitivity and class III (Sir2 homologues) which are quite distinct by their NAD^+ dependency and TSA insensitivity (Ruijter et al. Biochem.J. 370, 737-749, 2003; Khochbin et al. Curr Opin Gen Dev 11, 162-166, 2001; Verdin et al. Trends Gen 19, 286-293, 2003). HDAC 11 with Mr = 39kDa was cloned recently and displayed homology to class I and II family members (Gao et al. J Biol Chem 277,25748-25755, 2002). HATs and HDACs exist in large complexes together with transcription factor and platform proteins in cells (Fischle et al. Mol Cell 9, 45-47, 2002). Surprisingly, only 1-2% of all genes are regulated by histone acetylation (von Lint et al. Gene Expression 5, 245-253, 1996). Substrates different to histone proteins exist. For HDACs these include transcription factors like p53 and TFII E / or chaperones like Hsp90 (Johnstone & Licht, Cancer Cell 4, 13-18, 2003). Therefore the correct name for HDACs would be lysine-specific protein deacetylases. As a consequence of these findings, inhibitors of HDACs effect not only chromatin structure and gene transcription but also protein function and stability by regulating protein acetylation in general. In this regard, proteins involved in oncogenic transformation and malignant cell growth are of particular importance.

Different publications highlight the importance of histone acetylation for cancer development (reviewed by Kramer et al. Trends Endocrin Metabol 12, 294-300, 2001; Marks et al. Nature Cancer Rev 1, 194-202, 2001). These diseases include

(i) mutations of the HAT cAMP response element binding protein (CBP) associated with Rubinstein-Taybi syndrome, a cancer predisposition (Murata et al. Hum Mol Genet 10, 1071-1076, 2001),

(ii) aberrant recruitment of HDAC1 activity by transcription factors in acute promyelocytic leukemia (APL) by the PML-retinoic acid receptor α fusion gene (He et al. Nat genet 18, 126-135, 1998)

(iii) aberrant recruitment of HDAC activity by the overexpressed BCL6 protein in non-Hodgkins lymphoma (Dhordain et al. Nuceic Acid Res 26, 4645-4651, 1998) and finally

(iv) aberrant recruitment of HDAC activity by the AML-ETO fusion protein in acute myelogenous leukemia (AML M2 subtype; Wang et al. Proc Natl Acad Sci USA 95, 10860-10865, 1998). In this AML subtype, the recruitment of HDAC1 activity causally leads to gene silencing, a differentiation block and oncogenic transformation.

On the molecular level, a pleithora of published data with various HDAC inhibitors like Trichostatin A (TSA) showed that many cancer relevant genes are up- or down regulated. These include $p21^{CIP1}$, Cyclin E, transforming growth factor ß (TGFß), p53 or the von Hippel-Lindau (VHL) tumor suppressor genes, which are upregulated, whereas Bcl-XL, bcl2, hypoxia inducible factor (HIF)1α, vascular endothelial growth factor (VEGF) and cyclin A/D are down-regulated by HDAC inhibition (reviewed by Kramer et al. Trends Endocrin Metabol 12, 294-300, 2001). HDAC inhibitors arrest cells at G1 and G2/M within the cell cycle and deplete S-phase cells, as shown for Depsipeptide as an example (Sandor et al., British J Cancer 83, 817-825, 2000). HDAC inhibitory compounds induce p53 and caspase3/8 independent apoptosis and have broad anti-tumor activity. Anti-angiogenic activity was described also, which might be related to down-regulation of VEGF and HIF1α. In summary, HDAC inhibition effects tumor cells at different molecular levels and multiple cellular proteins are targeted.

Interestingly, HDAC inhibitors were found to induce cellular differentiation and this pharmacological activity might contribute to their anti-cancer activity as well. For example it was shown recently that suberoylanilide hydroxamic acid (SAHA) induces differentiation of breast cancer cell lines, exemplified by resynthesis of milk fat membrane globule protein (MFMG), milk fat globule protein and lipid (Munster et al. Cancer Res. 61, 8492, 2001).

There is growing rational for synergism of HDAC inhibitors with chemotherapeutic as well as target specific cancer drugs. For example, synergism was shown for SAHA with the kinase / cdk inhibitor flavopiridol (Alemenara et al. Leukemia 16, 1331-1343, 2002), for LAQ-824 with the bcr-abl kinase inhibitor Glivec in CML cells (Nimmanapalli et al. Cancer Res. 63, 5126-5135, 2003) and for SAHA and Trichostatin A (TSA) with etoposide (VP16), cisplatin and doxorubicin (Kim et al. Cancer Res. 63, 7291-7300, 2003). Also it was shown that HDAC inhibition causes reexpression of estrogen or

androgen receptors in breast and prostate cancer cells with the potential to resensitize these tumors to anti-hormone therapy (Yang et al. Cancer Res. 60, 6890-6894, 2000; Nakayama et al. Lab Invest 80, 1789-1796, 2000).

HDAC inhibitors from various chemical classes were described in the literature with four most important classes, namely (i) hydroxamic acid analogs, (ii) benzamide analogs, (iii) cyclic peptides / peptolides and (iv) fatty acid analogs. A comprehensive summary of known HDAC inhibitors was published recently (Miller et al. J Med Chem 46, 5097-5116, 2003). There is only limited data published regarding specificity of these histone deacetylase inhibitiors. In general most hydroxamate based HDI are not specific regarding class I and II HDAC enzymes. But there are exceptions like the experimental HDI Tubacin, selective for the class II enzyme HDAC 6 (Haggarty et al. Proc natl Acad Sci USA 100, 4389-4394, 2003). So far it is not clear if specificity towards HDAC class I or II enzymes or a defined single isoenzyme should be superior regarding therapeutic efficacy and index.

Clinical studies in cancer with HDAC inhibitors are on-going, namely with SAHA (Aton Pharma), Valproic acid / G2M777 (G2M Cancer Drugs), FK228 / Depsipeptide (NCI / Fujisawa-Klinge), MS275 (Mitsui / Schering Japan), LAQ-824 (Novartis), CI-994 (Pfizer) and Pivaloyloxymethylbutyrate / Pivanex (Titan Pharmaceuticals). These studies showed first evidence of clinical efficacy, highlighted recently by partial and complete responses with FK228 / Depsipeptide in patients with peripheral T-cell lymphoma (Plekarz et al. Blood, 98, 2865-2868, 2001).

Recent publications also showed possible medical use of HDAC inhibitors in disease different to cancer. These diseases include systemic lupus erythematosus (Mishra et a. J Clin Invest 111, 539-552, 2003), rheumatoid arthritis (Chung et al. Mol Therapy 8, 707-717, 2003), inflammatory diseases (Leoni et al. Proc Natl Acad Sci USA 99, 2995-3000, 2002) and neurodegenerative diseases like Huntington´s disease (Steffan et al. Nature 413, 739-743, 2001, Hockly et al. Proc Natl Acad Sci USA 100(4):2041-6, 2003).

Cancer chemotherapy was established based on the concept that cancer cells with uncontrolled proliferation and a high proportion of cells in mitosis are killed preferentially. Standard cancer chemotherapeutic drugs finally kill cancer cells upon induction of programmed cell death ("apoptosis") by targeting basic cellular processes and molecules, namely RNA/DNA (alkylating and carbamylating agents, platin analogs and topoisomerase inhibitors), metabolism (drugs of this class are named anti-metabolites) as well as the mitotic spindle apparatus (stabilizing and destabilizing tubulin inhibitors). Inhibitors of histone deacetylases (HDIs) constitute a new class of anti cancer drugs with differentiation and apoptosis inducing activity. By targeting histone deacetylases, HDIs effect histone (protein) acetylation and chromatin structure, inducing a complex transcriptional reprogramming, exemplified by reactivation of tumor suppressor genes and repression of oncogenes. Beside effecting acetylation of N-terminal lysine residues in core histone proteins, non-histone targets important for cancer cell biology like heat-shock-protein 90 (Hsp90) or the p53 tumor suppressor protein exist. The medical use

of HDIs might not be restricted to cancer therapy, since efficacy in models for inflammatory diseases, rheumatoid arthritis and neurodegeneration was shown.

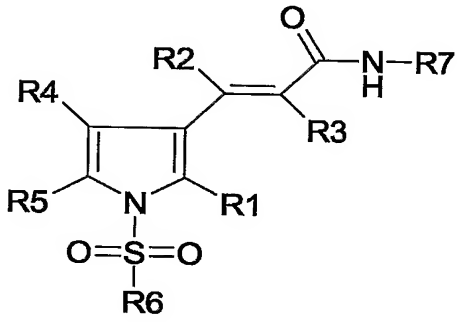
Prior Art

Benzoyl or acetyl substituted pyrrolyl propenamides are described in the public literature as HDAC-inhibitors, whereas the connectivity of the acyl-group is at position 2 or 3 of the pyrrole scaffold. (Mai et.al., Journal Med.Chem. 2004, Vol. 47, No. 5, 1098-1109). Further pyrrolyl substituted hydroxamic acid derivatives are described in US4960787 as lipoxygenase inhibitors or in US6432999 as cyclooxygenase inhibitors.

Description of the invention

It has now been found that the N-sulphonylpyrrole derivatives, which are described in greater details below, are inhibitors of histone deactylases and have surprising and particularly advantageous properties.

The invention thus relates to compounds of formula I



(I)

in which

R1 is hydrogen, 1-4C-alkyl, halogen, or 1-4C-alkoxy,

R2 is hydrogen or 1-4C-alkyl,

R3 is hydrogen or 1-4C-alkyl,

R4 is hydrogen, 1-4C-alkyl, halogen, or 1-4C-alkoxy,

R5 is hydrogen, 1-4C-alkyl, halogen, or 1-4C-alkoxy,

R6 is -T1-Q1, in which

T1 is a bond, or 1-4C-alkylene,

Q1 is Ar1, Aa1, Hh1, or Ah1, in which

Ar1 is phenyl, or R61- and/or R62-substituted phenyl, in which

R61 is 1-4C-alkyl, or -T2-N(R611)R612, in which

T2 is a bond, 1-4C-alkylene, or 2-4C-alkylene interrupted by oxygen,

R611 is hydrogen, 1-4C-alkyl, hydroxy-2-4C-alkyl, 1-4C-alkoxy-2-4C-alkyl, phenyl-1-4C-alkyl, or Har1-1-4C-alkyl, in which

Har1 is optionally substituted by R6111 and/or R6112, and is a monocyclic or fused bicyclic 5- to 10-membered unsaturated heteroaromatic ring comprising one to three heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and sulfur, in which

R6111 is halogen, or 1-4C-alkyl,

R6112 is 1-4C-alkyl,

R612 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy-2-4C-alkyl or hydroxy-2-4C-alkyl,

R62 is 1-4C-alkyl, 1-4C-alkoxy, halogen, cyano, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkylcarbonylamino, or 1-4C-alkylsulphonylamino,

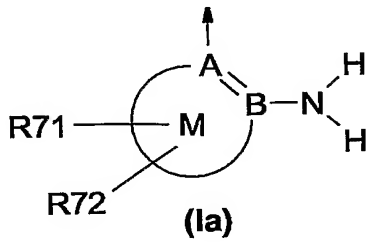
Aa1 is a bisaryl radical made up of two aryl groups,
which are selected independently from a group consisting of phenyl and naphthyl, and
which are linked together via a single bond,

Hh1 is a bisheteroaryl radical made up of two heteroaryl groups,
which are selected independently from a group consisting of monocyclic 5- or 6-membered heteroaryl radicals comprising one or two heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and sulfur, and
which are linked together via a single bond,

Ah1 is a heteroaryl-aryl radical or an aryl-heteroaryl radical made up of a heteroaryl group selected from a group consisting of monocyclic 5- or 6-membered heteroaryl radicals comprising one or two heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and sulfur, and an aryl group selected from a group consisting of phenyl and naphthyl, whereby said heteroaryl and aryl groups are linked together via a single bond,

R7 is hydroxyl, or Cyc1, in which

Cyc1 is a ring system of formula Ia



(Ia)

in which

A	is C (carbon),
B	is C (carbon),
R71	is hydrogen, halogen, 1-4C-alkyl, or 1-4C-alkoxy,
R72	is hydrogen, halogen, 1-4C-alkyl, or 1-4C-alkoxy,
M	with inclusion of A and B is either a ring Ar2 or a ring Har2, in which
Ar2	is a benzene ring,
Har2	is a monocyclic 5- or 6-membered unsaturated heteroaromatic ring comprising one to three heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and sulfur,

and the salts of these compounds.

1-4C-Alkyl represents a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl and preferably the ethyl and methyl radicals.

2-4C-Alkyl represents a straight-chain or branched alkyl radical having 2 to 4 carbon atoms. Examples which may be mentioned are the butyl, isobutyl, sec-butyl, tert-butyl, propyl, isopropyl and preferably the ethyl and propyl radicals.

1-4C-Alkylene is a branched or, particularly, straight chain alkylene radical having 1 to 4 carbon atoms. Examples which may be mentioned are the methylene ($-CH_2-$), ethylene ($-CH_2-CH_2-$), trimethylene ($-CH_2-CH_2-CH_2-$) and the tetramethylene ($-CH_2-CH_2-CH_2-CH_2-$) radical.

2-4C-Alkylene interrupted by oxygen stands for a straight chain alkylene radical having 1 to 4 carbon atoms which is suitably interrupted by an oxygen atom such as, for example, the [$-CH_2-CH_2-O-CH_2-CH_2-$] radical.

1-4C-Alkoxy represents radicals which, in addition to the oxygen atom, contain a straight-chain or branched alkyl radical having 1 to 4 carbon atoms. Examples which may be mentioned are the butoxy, isobutoxy, sec-butoxy, tert-butoxy, propoxy, isopropoxy and preferably the ethoxy and methoxy radicals.

1-4C-Alkoxy-1-4C-alkyl represents one of the abovementioned 1-4C-alkyl radicals, which is substituted by one of the abovementioned 1-4C-alkoxy radicals. Examples which may be mentioned are the methoxymethyl, the methoxyethyl and the isopropoxyethyl radicals, particularly the 2-methoxyethyl and the 2-isopropoxyethyl radicals.

1-4C-Alkoxy-2-4C-alkyl represents one of the abovementioned 2-4C-alkyl radicals, which is substituted by one of the abovementioned 1-4C-alkoxy radicals. Examples which may be mentioned

are the methoxyethyl, ethoxyethyl and the isopropoxyethyl radicals, particularly the 2-methoxyethyl, the 2-ethoxyethyl and the 2-isopropoxyethyl radicals.

Hydroxy-2-4C-alkyl represents one of the abovementioned 2-4C-alkyl radicals, which is substituted by a hydroxy radical. An example which may be mentioned is the 2-hydroxyethyl radical.

Phenyl-1-4C-alkyl stands for one of the abovementioned 1-4C-alkyl radicals, which is substituted by a phenyl radical. Examples which may be mentioned are the benzyl and the phenethyl radicals.

Halogen within the meaning of the invention is bromine or, in particular, chlorine or fluorine.

1-4C-Alkylcarbonyl represents a radical which, in addition to the carbonyl group, contains one of the abovementioned 1-4C-alkyl radicals. An example which may be mentioned is the acetyl radical.

1-4C-Alkylcarbonylamino represents an amino radical which is substituted by one of the abovementioned 1-4C-alkylcarbonyl radicals. An example which may be mentioned is the acetamido radical [$CH_3C(O)$-NH-].

1-4C-Alkylsulphonylamino is, for example, the propylsulfonylamino [$C_3H_7S(O)_2NH$-], the ethylsulfonylamino [$C_2H_5S(O)_2NH$-] and the methylsulfonylamino [$CH_3S(O)_2NH$-] radical.

Aa1 is a bisaryl radical made up of two aryl groups,
which are selected independently from a group consisting of phenyl and naphthyl, and
which are linked together via a single bond.
Aa1 may include, without being restricted thereto, the biphenyl radical, e.g. the 1,1'-biphen-4-yl radical.

Hh1 is a bisheteroaryl radical made up of two heteroaryl groups,
which are selected independently from a group consisting of monocyclic 5- or 6-membered heteroaryl radicals comprising one or two heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and sulfur, and
which are linked together via a single bond.
Hh1 may include, without being restricted thereto, the bithiophenyl radical.

Ah1 is a heteroarylaryl radical or an arylheteroaryl radical made up of a heteroaryl group selected from a group consisting of monocyclic 5- or 6-membered heteroaryl radicals comprising one or two heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and sulfur, and an aryl group selected from a group consisting of phenyl and naphthyl, whereby said heteroaryl and aryl groups are linked together via a single bond.

Ah1 may include, without being restricted thereto, the phenyl-thiophenyl or the thiophenyl-phenyl radical.

Har1 is optionally substituted by R6111 and/or R6112, and is a monocyclic or fused bicyclic 5- to 10-membered unsaturated (heteroaromatic) heteroaryl radical comprising one to three heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and sulfur. In one detail, fused, in particular benzo-fused, bicyclic 9- or 10-membered heteroaryl radicals comprising one to three, in particular one or two, heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and sulfur, are to be mentioned. Examples of Har1 include, withouit being restricted thereto, thiophenyl, furanyl, pyrrolyl, oxazolyl, isoxazolyl, pyrazolyl, imidazolyl, thiazolyl, isothiazolyl, triazolyl, oxadiazolyl, thiadiazolyl, pyridinyl, pyrimidinyl, pyrazinyl or pyridazinyl; and, in particular, the stabile benzo-fused derivatives thereof, such as e.g. benzothiophenyl, benzofuranyl, indolyl, benzoxazolyl, benzothiazolyl, indazolyl, benzimidazolyl, benzisoxazolyl, benzisothiazolyl, benzofurazanyl, quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, phthalazinyl or cinnolinyl; and purinyl, indolizinyl, naphthyridinyl or pteridinyl.

As further examples of Har1, the R6111- and/or R6112-substituted derivatives of the abovementioned exemplary Har1 radicals may be mentioned.

Har1-1-4C-alkyl stands for one of the abovementioned 1-4C-alkyl radicals, such as e.g. methyl, ethyl or propyl, substituted by one of the abovementioned Har1 radicals, such as e.g. imidazolyl, benzimidazolyl, indolyl or pyrrolyl and the like or the substituted derivatives thereof. As examples may be mentioned, without being restricted thereto, pyridinylmethyl, imidazolylmethyl, pyrrolylmethyl, 2-imidazolylethyl (e.g. 2-imidazol-5-yl-ethyl), 2-pyridinylethyl, 3-(benzofuran-2-yl)propyl, 3-(benzimidazol-2-yl)propyl, 2-indolylethyl (e.g. 2-indol-2-yl-ethyl), indolylmethyl (e.g. indol-2-yl-methyl), 2-benzimidazolylethyl (e.g. 2-benzimidazol-2-ylethyl), benzimidazolylmethyl (e.g. benzimidazol-2-yl-methyl), and the like.

Har2 stands for a monocyclic 5- or 6-membered unsaturated heteroaromatic ring comprising one to three heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and sulfur. Har2 may include, without being restricted thereto, thiophene, oxazole, isoxazole, thiazole, isothiazole, imidazole, pyrazole, triazole, thiadiazole, oxadiazole, pyridine, pyrimidine, pyrazine or pyridazine.

Cyc1 stands for a ring system of formula Ia, which is bonded to the nitrogen atom of the carboxamide group via the moiety A. Cyc1 may include, without being restricted thereto, 2-aminophenyl substituted by R71 and/or R72.

Suitable salts for compounds of the formula I - depending on substitution - are all acid addition salts or all salts with bases. Particular mention may be made of the pharmacologically tolerable inorganic and organic acids and bases customarily used in pharmacy. Those suitable are, on the one hand, water-

insoluble and, particularly, water-soluble acid addition salts with acids such as, for example, hydrochloric acid, hydrobromic acid, phosphoric acid, nitric acid, sulphuric acid, acetic acid, citric acid, D-gluconic acid, benzoic acid, 2-(4-hydroxybenzoyl)benzoic acid, butyric acid, sulphosalicylic acid, maleic acid, lauric acid, malic acid, fumaric acid, succinic acid, oxalic acid, tartaric acid, embonic acid, stearic acid, toluenesulphonic acid, methanesulphonic acid or 3-hydroxy-2-naphthoic acid, the acids being employed in salt preparation - depending on whether a mono- or polybasic acid is concerned and depending on which salt is desired - in an equimolar quantitative ratio or one differing therefrom.

On the other hand, salts with bases are - depending on substitution - also suitable. As examples of salts with bases are mentioned the lithium, sodium, potassium, calcium, aluminium, magnesium, titanium, ammonium, meglumine or guanidinium salts, here, too, the bases being employed in salt preparation in an equimolar quantitative ratio or one differing therefrom.

Pharmacologically intolerable salts, which can be obtained, for example, as process products during the preparation of the compounds according to the invention on an industrial scale, are converted into pharmacologically tolerable salts by processes known to the person skilled in the art.

According to expert's knowledge the compounds of the invention as well as their salts may contain, e.g. when isolated in crystalline form, varying amounts of solvents. Included within the scope of the invention are therefore all solvates and in particular all hydrates of the compounds of formula I as well as all solvates and in particular all hydrates of the salts of the compounds of formula I.

The substituents R61 and R62 of compounds of formula I can be attached in the ortho, meta or para position with respect to the binding position in which the phenyl ring is bonded to T1, whereby preference is given to the attachement in the meta or, particularly, in the para position.

Compounds according to the present invention more worthy to be mentioned are those compounds of formula I
in which

R1	is hydrogen, or 1-4C-alkyl,
R2	is hydrogen, or 1-4C-alkyl,
R3	is hydrogen, or 1-4C-alkyl,
R4	is hydrogen, or 1-4C-alkyl,
R5	is hydrogen, or 1-4C-alkyl,
R6	is -T1-Q1, in which
T1	is a bond, or 1-4C-alkylene,
Q1	is Ar1, or Aa1, in which
Ar1	is phenyl, or R61-substituted phenyl, in which
R61	is 1-4C-alkyl, or -T2-N(R611)R612, in which
T2	is a bond, or 1-4C-alkylene,

R611 is hydrogen, 1-4C-alkyl, or Har1-1-4C-alkyl, in which
Har1 is imidazolyl, benzimidazolyl, indolyl or pyrrolyl,
R612 is hydrogen, or 1-4C-alkyl,
Aa1 is a biphenyl radical,
R7 is hydroxyl, or 2-aminophenyl,
and the salts of these compounds.

Compounds according to the present invention in particular worthy to be mentioned are those compounds of formula I
in which
R1 is hydrogen,
R2 is hydrogen,
R3 is hydrogen,
R4 is hydrogen,
R5 is hydrogen,
R6 is -T1-Q1, or biphenyl, in which
T1 is a bond, or 1-2C-alkylene,
Q1 is Ar1, in which
Ar1 is phenyl, or R61-substituted phenyl, in which
R61 is 1-4C-alkyl, or -T2-N(R611)R612, in which
T2 is a bond, or 1-2C-alkylene,
R611 is 1-4C-alkyl, or Har1-1-2C-alkyl, in which
Har1 is benzimidazolyl or indolyl,
R612 is 1-4C-alkyl,
R7 is hydroxyl, or 2-aminophenyl,
and the salts of these compounds.

Compounds according to the present invention in more particular worthy to be mentioned are those compounds of formula I
in which
R1 is hydrogen,
R2 is hydrogen,
R3 is hydrogen,
R4 is hydrogen,
R5 is hydrogen,
R6 is -T1-Q1, biphenyl, or benzyl, in which
T1 is a bond,
Q1 is Ar1, in which
Ar1 is R61-substituted phenyl, in particular 4-(R61)-phenyl, in which
R61 is methyl, dimethylamino, or -T2-N(R611)R612, in which

T2 is methylene,
R611 is methyl or 2-(indol-2-yl)ethyl,
R612 is methyl,
R7 is hydroxyl, or 2-aminophenyl,
and the salts of these compounds.

An embodiment of the compounds according to the present invention relates to those compounds of formula I, in which R1, R2, R3, R4 and R5 are all hydrogen.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which R7 is hydroxyl.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which R7 is Cyc1, whereby in a subembodiment thereof Cyc1 is 2-phenyl.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which R6 is Aa1.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which R6 is Ar1 or -CH_2-Ar1.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which Ar1 is R61-substituted phenyl.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which R1, R2, R3, R4 and R5 are all hydrogen, and R7 is hydroxyl.

A further embodiment of the compounds according to the present invention relates to those compounds of formula I, in which R1, R2, R3, R4 and R5 are all hydrogen, and R7 is Cyc1.

The compounds according to the present invention can be prepared, for example, as shown in the reaction scheme below and according to the reaction steps specified as follows, or, particularly, in a manner as described by way of example in the following examples, or analogously or similarly thereto using preparation procedures and synthesis strategies known to the person skilled in the art.

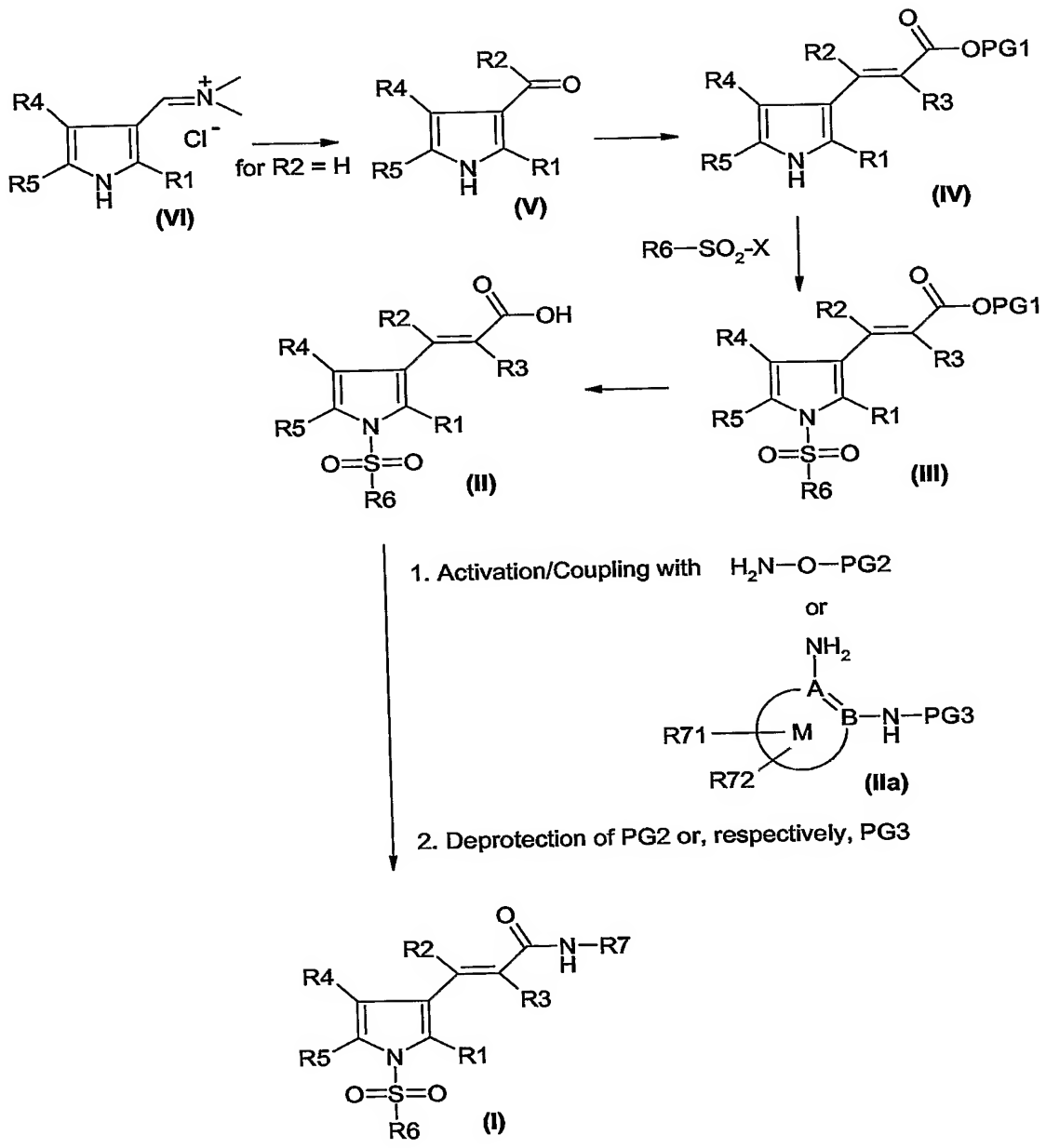
In reaction scheme 1 the carbon chain of compounds of formula V, in which R1, R2, R4 and R5 have the meanings mentioned above, is lengthened, for example, by a condensation reaction (with a malonic acid derivative) or by a Wittig or Julia reaction or, particularly in the case when R2 is hydrogen, by a Horner-Wadsworth-Emmons reaction (with a β-(alkoxycarbonyl)-phosphonic acid dialkyl ester) to obtain compounds of formula IV, in which R1, R2, R3, R4 and R5 have the meanings

mentioned above and PG1 stands for a suitable protective carboxyl group, for example tert-butyl or one of those art-known protective groups mentioned in "Protective Groups in Organic Synthesis" by T. Greene and P. Wuts (John Wiley & Sons, Inc. 1999, 3rd Ed.) or in "Protecting Groups (Thieme Foundations Organic Chemistry Series N Group" by P. Kocienski (Thieme Medical Publishers, 2000).

Compounds of formula V, in which R1, R2, R4 and R5 have the meanings mentioned above, are known, or can be prepared according to art-known procedures, or can be obtained as described in the following examples for the case that R2 is hydrogen from compounds of formula VI.

Compounds of formula VI are known or are accessible in a known manner or as described in the following examples.

Reaction scheme 1



Compounds of formula IV, in which R1, R2, R3, R4 and R5 have the meanings mentioned above and PG1 stands for a said suitable protective group, can be reacted with compounds of formula R6-SO_2-X, in which R6 has the meanings mentioned above and X is a suitable leaving group, such as e.g. chlorine, to give the corresponding compounds of formula III.

In the next reaction step, the protective group PG1 of compounds of formula III can be removed in a manner as described in the following examples or according to an art-known manner to afford compounds of formula II.

Compounds of formula R6-SO_2-X are known or can be prepared in a known manner.

Compounds of formula II, in which R1, R2, R3, R4, R5 and R6 have the meanings given above, can be coupled with compounds of formulae H_2N-O-PG2, in which PG2 is a suitable oxygen protective group such as e.g. a suitable silyl or tetrahydropyran-2-yl protective group, or IIa, in which PG3 stands for a suitable nitrogen protective group such as e.g. the tert-butyloxycarbonyl protective group, by reaction with amide bond linking reagents optionally in the presence of coupling additives known to the person skilled in the art. Exemplary amide bond linking reagents known to the person skilled in the art which may be mentioned are, for example, carbodiimides (e.g. dicyclohexylcarbodiimide or, preferably, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride), azodicarboxylic acid derivatives (e.g. diethyl azodicarboxylate), uronium salts [e.g. O-(benzotriazol-1-yl)-N,N,N',N'-tetra-methyluronium tetrafluoroborate or O-(benzotriazol-1yl)-N,N,N',N'-tetramthyl-uronium-hexafluorophosphate] and N,N'-carbonyldiimidazole.

Alternatively, compounds of formula II can be activated prior to the coupling reaction by forming an acid halide or acid anhydride optionally in an in-situ procedure without isolating the acid halide or acid anhydride.

Compounds of formulae H_2N-O-PG2 or IIa are known or can be prepared according to art-known processes.

Removal of the protective groups PG2 or PG3 can be obtained in a manner known for the person skilled in the art or as described in the following examples to give compounds of formula I, in which R1, R2, R3, R4, R5, R6 and R7 have the meanings mentioned above.

It is moreover known to the person skilled in the art that if there are a number of reactive centers on a starting or intermediate compound it may be necessary to block one or more reactive centers temporarily by protective groups in order to allow a reaction to proceed specifically at the desired reaction center. A detailed description for the use of a large number of proven protective groups is found, for example, in "Protective Groups in Organic Synthesis" by T. Greene and P. Wuts (John Wiley & Sons, Inc. 1999, 3rd Ed.) or in "Protecting Groups (Thieme Foundations Organic Chemistry Series N Group" by P. Kocienski (Thieme Medical Publishers, 2000).

The isolation and purification of the substances according to the invention is carried out in a manner known per se, e.g. by distilling off the solvent in vacuo and recrystallizing the resulting residue from a

suitable solvent or subjecting it to one of the customary purification methods, such as, for example, column chromatography on suitable support material.

Salts are obtained by dissolving the free compound in a suitable solvent (e.g. a ketone, such as acetone, methyl ethyl ketone or methyl isobutyl ketone, an ether, such as diethyl ether, tetrahydrofuran or dioxane, a chlorinated hydrocarbon, such as methylene chloride or chloroform, or a low molecular weight aliphatic alcohol such as ethanol or isopropanol) which contains the desired acid or base, or to which the desired acid or base is then added. The salts are obtained by filtering, reprecipitating, precipitating with a nonsolvent for the addition salt or by evaporating the solvent. Salts obtained can be converted by alkalization or by acidification into the free compounds, which in turn can be converted into salts. In this way, pharmacologically intolerable salts can be converted into pharmacologically tolerable salts.

Suitably, the conversions mentioned in this invention can be carried out analogously or similarly to methods which are familiar per se to the person skilled in the art.

The person skilled in the art knows on the basis of his/her knowledge and on the basis of those synthesis routes, which are shown and described within the description of this invention, how to find other possible synthesis routes for compounds of the formula I. All these other possible synthesis routes are also part of this invention.

Having described the invention in detail, the scope of the present invention is not limited only to those described characteristics or embodiments. As will be apparent to persons skilled in the art, modifications, analogies, variations, derivations, homologisations and adaptations to the described invention can be made on the base of art-known knowledge and/or, particularly, on the base of the disclosure (e.g. the explicite, implicite or inherent disclosure) of the present invention without departing from the spirit and scope of this invention.

The following examples serve to illustrate the invention further without restricting it. Likewise, further compounds of the formula I, whose preparation is not explicitly described, can be prepared in an analogous manner or in a manner familiar per se to the person skilled in the art using customary process techniques.

The compounds which are mentioned as final products in the following examples as well as their salts are a preferred subject of the present invention.

In the examples, MS stands for mass spectrum, M for molecular ion, TSP for Thermospray Ionization, ESI for Electrospray Ionization, EI for Electron Ionization, h for hours, min for minutes. Other abbreviations used herein have the meanings customary per se to the person skilled in the art.

Examples

Final products

1. (E)-N-Hydroxy-3-[1-(toluene-4-sulfonyl)-1-H-pyrrol-3-yl]-acrylamide

0.231 g of (E)-3-[1-(toluene-4-sulfonyl)-1H-pyrrol-3yl]-acrylic acid (compound A1) are dissolved in 8 ml of dichloromethane at room temperature. Then 50 µl of N,N-dimethylformamide (DMF) are added, 0.275 g of oxalic acid chloride dissolved in 2 ml of dichoromethane are added dropwise and stirred for 1.5 hour. To the solution are added 0.439 g of O-(trimethylsilyl)hydroxylamine and stirred for 15 minutes. Then 20 ml of aqueous hydrochloric acid (1 M strength) are added and extracted with ethyl acetate. The combined organic phase is dried over sodium sulfate. Afterwards it is filtered and evaporated under vacuo. The crude product is purified by silica gel flash chromatography using a gradient of dichloromethane and methanol from 98:2 to 6:4 to yield 0.050 g of the title compound as a white solid.

MS (TSP): 307.0 (MH^+, 100%)

^{1}H-NMR (DMSO-d6): ^{1}H-NMR (DMSO-d6): 2.37 (s, 3H); 6,12 (d, J = 15.9 Hz, 1H); 6.54 (m, 1H); 7.25 (m, J = 16.1 Hz, 2H); 7.42 (d, J = 8.1 Hz, 2H); 7.79 (m, 1H); 7.85 (d, J = 8.2 Hz, 2H); 8.96 (bs, exchangeable, 1H); 10.61 (bs, exchangeable, 1H)

2. N-Hydroxy-3-(1-phenylmethanesulfonyl-1H-pyrrol-3-yl)-acrylamide

0.189 g of (E)-3-(1-phenylmethanesulfonyl-1H-pyrrol-3-yl)-N-(tetrahydropyran-2-yloxy)-acrylamide (compound A2) are dissolved in 50 ml of a methanol/water (3/2) solution. Then 0.102 g of the acidic ion exchange resin amberlyst IR15 are added and the mixture is stirred for 91 hours at ambient temperature. The mixture is filtered. The filtrate is evaporated. The residue is crystallized from methanol to give 0.144 g of the title compound as white crystals.

MS (TSP): 307.0 (MH^+, 100%)

^{1}H-NMR (DMSO-d6): 5.00 (s, 2H); 6.11 (d, J = 15.7 Hz, 1H); 6.50 (m, 1H); 6.96 (m, 1H); 7.11 (m, 2H); 7.32 (m, J = 17 Hz, 5H); 8.90 (s, exchangeable, 1H); 10.60 (s, exchangeable, 1H)

3. (E)-3-[1-(Biphenyl-4-sulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide

The method used for preparation of this compound is analogous to the method described for compound 2.

Starting materials: (E)-3-(1-(biphenyl-4-sulfonyl)-1H-pyrrol-3-yl)-N-(tetrahydro-pyran-2-yloxy)-acrylamide (compound A3) (0.150 g), methanol/water 3/2 (50 ml), amberlyst IR15 (0.300 g). Reaction conditions: room temperature, 34 hours.

Yield: 0.041 g, pale grey crystals

MS (ESI): 381.1 (MH^+-CH_3NO_2, 100%)

^{1}H-NMR (DMSO-d6): 6.14 (d, J = 15.8 Hz, 1H); 6.58 (m, 1H); 7.31 (d, J = 15.7 Hz, 1H); 7.43 (m, J = 6.9 Hz, 4H); 7.70 (m, J =6.6 Hz, 3H); 7.91 (d, J = 8.0 Hz, 2H); 8.02 (d, J = 8.1 Hz, 2H); 8.92 (s, exchangeable, 1H); 10.60 (s, exchangeable, 1H)

4. (E)-3-[1-(4-Dimethylamino-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide

The method used for preparation of this compound is analogous to the method described for compound 2.

Starting materials: (E)-3-[1-(4-dimethylamino-benzene sulfonyl)-1H-pyrrol-3-yl]-N-(tetrahydro-pyran-2-yloxy)-acrylamide (compound A4) (0.200 g), methanol/water 3/2 (50 ml), amberlyst IR15 (0.402 g).

Reaction conditions: room temperature, 34 hours.

Yield: 0.098 g, pale red crystals

MS (ESI): 336.0 (MH^+, 100%)

^{1}H-NMR (DMSO-d6): 6.10 (m, J = 16.5 Hz 1H); 6.49 (m, 1H); 6.75 (d, J = 9.2 Hz, 2H); 7.24 (m, 2H); 7.64 (m, J_1 = 8.6 Hz, J_2 = 17.7 Hz, 3H); 8.89 (bs, exchangeable, 1H), 10.59 (bs, exchangeable, 1H)

5. (E)-N-(2-Amino-phenyl)-3-[1-(toluene-4-sulfonyl)-1H-pyrrol-3-yl]-acrylamide

0.116 g of (2-{(E)-3-[1-(toluene-4-sulfonyl)-1-H-pyrrol-3-yl]-allanoylamino}-phenyl)-carbamic acid *tert*-butyl ester (compound A5) are dissolved in 20 ml of dichloromethane at ambient temperature. 2 ml of trifluoroacetic acid (TFA) are added and the solution is stirred for 93 hour. The solvent is evaporated to dryness and to the residue are added 25 ml of water. The water phase is extracted exhaustively with ethyl acetate. Afterwards the combined organic phase are dried over sodium sulfate and filtered. The filtrate is evaporated under vacuo. Then the residue is crystallized from methanol to give 0.050 g of the title compound as white crystals.

MS (ESI): 382.0 (MH^+, 100%)

^{1}H-NMR (DMSO-d6): 2.38 (s, 3H); 4.48 (s, exchangeable, 2H); 6.55 (m, 3H); 6.71 (m, 1H); 6.90 (m, 1H); 7.40 (m, J = 8.1 Hz, 5H); 7.70 (m, 1H); 7,89 (d, J = 8.3 Hz, 2H); 9.20 (s, exchangeable, 1H)

6. (E)-N-(2-Amino-phenyl)-3-(1-phenylmethanesulfonyl-1H-pyrrol-3-yl)-acrylamide

The method used for preparation of this compound is analogous to the method described for compound 5 with the exception that the product is purified by silica gel flash chromatography using a gradient of dichloromethane/methanol from 99:1 to 95:5.

Starting materials: {2-[(E)-3-[1-(phenylmethanesulfonyl-1-H-pyrrol-3-yl)-allanoylamino]-phenyl}-carbamic acid *tert*-butyl ester (compound A6) (0.146 g), CH_2Cl_2 (20 ml), TFA (2 ml). Reaction conditions: room temperature, 65 hours.

Yield: 0.037 g, white crystals

MS (ESI): 382.0 (MH^+)

^{1}H-NMR (DMSO-d6): 4.90 (s, 2H); 5.01 (s, exchangeable, 1H); 6.58 (m, J = 5.7 Hz, 3H); 6.74 (m, J = 6.7 Hz, 2H); 6.90 (m, 1H); 7.01 (m, 1H); 7.11 (m, J = 5.6, 2H); 7.34 (m, J_1 = 5.7 Hz, J_2 = 6.7 Hz, 5H); 9.25 (s, exchangeable, 1H)

7. (E)-N-(2-Amino-phenyl)-3-[1-(biphenyl-4-sulfonyl)-1H-pyrrol-3-yl]-acrylamide

The method used for preparation of this compound is analogous to the method described for compound 5.

Starting materials: (2-{(E)-3-[1-(biphenyl-4-sulfonyl)-1H-pyrrol-3-yl]-allanoylamino}-phenyl)-carbamic acid *tert*-butyl ester (compound A7) (0.460 mmol), CH_2Cl_2 (50 ml), TFA (5 ml). Reaction conditions: room temperature, 18 hours.
Yield: 0.061 g, white crystals
MS (ESI): 444.0 (MH^+)
^{1}H-NMR (DMSO-d6): 4.90 (bs, exchangeable, 2H); 6.58 (m, J_1 = 51.4 Hz, J_2 = 7.5 Hz, 3H); 6.71 (m, J_1 = 1.4 Hz, J_2 = 6.6 Hz, 1H); 6.90 (m, J_1 = 1.4 Hz, J_2 = 6.6 Hz, 1H); 7.40 (m, J_1 = 7.5 Hz, J_2 = 7.7 Hz, 6H); 7.78 (m, J = 7.7 Hz, 3H); 7.95 (d, J = 8.6 Hz, 2H); 8.08 (d, J = 8.8 Hz, 2H); 9.23 (s, exchangeable, 1H)

8. (E)-N-(2-Amino-phenyl)-3-[1-(4-dimethylamino-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylamide

The method used for preparation of this compound is analogous to the method described for compound 5 with the exception that the product is purified by crystallization from ethyl acetate.
Starting materials: (2-{(E)-3-[1-(4-dimethylamino-benzenesulfonyl)-1H-pyrrol-3-yl]-allanoylamino}-phenyl)-carbamic acid *tert*-butyl ester (compound A8) (0.141 g), CH_2Cl_2 (10 ml), TFA (1 ml). Reaction conditions: room temperature, 20 hours.
Yield: 0.109 g, pale red crystals
MS (ESI): 411.0 (MH^+, 100%)
^{1}H-NMR (DMSO-d6): 3.00 (s, 6H); 3.97 (s, exchangeable, 2H); 6.79 (m, J= 15.4 Hz, 2H); 6.79 (d, J= 9.2 Hz, 2H); 7.04 (m, J_1 = 2.7 Hz, J_2 = 8.7 Hz, J_3= 15.5 Hz, 3H); 7.40 (m, J_1 = 15.6 Hz, J_2 = 8.6 Hz, 3H) 7.70 (m, J_1 = 2.9 Hz, J_2 = 9.2 Hz, 3H) 9.74 (s, exchangeable, 1H)

9. (E)-N-Hydroxy-3-(1-[4-(([2-(1H-indol-2-yl)-ethyl]-methyl-amino)-methyl)-benzene sulfonyl] -1H-pyrrol-3-yl)-acrylamide

81 mg of (E)-3-(1-[4-(([2-(1H-indol-2-yl)-ethyl]-methyl-amino)-benzenesulfonyl]-1H-pyrrol-3-yl)-N-(tetrahydropyran-2-yloxy)-acrylamide (compound A9) are dissolved in 5 ml of methanol. After addition of 15 ml of 0.1N hydrochloric acid the mixture is stirred for 21 hour. Then the reaction mixture is evaporated. The residue is washed with ethyl acetate and dried under vacuum at –50°C.
Yield: 55 mg, pale yellow solid

10. (E)-3-[1-(4-Dimetylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-hydroxy-acrylamide

The method used for to preparation of this compound is analogous to the method described for compound 9.
Starting material: (E)-3-[1-(4-Dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-N-tetrahydro-pyran-2-yloxy)-acrylamide (compound A10)

Starting materials

A1 (E)-3-[1-(Toluene-4-sulfonyl)-1H-pyrrol-3yl]-acrylic acid

1.60 g of (E)-3-[1-(toluene-4-sulfonyl)-1H-pyrrol-3yl]-acrylic acid *tert*-butyl ester (compound C1) are dissolved in 70 ml of dichloromethane at ambient temperature. Then 7 ml of trifluoroatetic acid (TFA) are added and stirred for 4 hours. The solvent is evaporated to dryness and to the residue are added 30 ml of water. The water phase is extracted exhaustively with ethyl acetate. Then the organic phase is dried over sodium sulfate. The filtrate is evaporated and dried under vacuo to give 0.951 g of the title compound as a pale grey solid.

MS (TSP): 290.0 ($M\text{-}H^+$, 100%)

^{1}H-NMR (DMSO-d6): 2.36 (s, 3H); 6,20 (d, J = 15.9 Hz, 1H); 6.74 (m, J = 3.1 Hz, 1H); 7.41 (m, J_1 = 3.1 Hz, J_2 = 8.2 Hz, J_3 = 16.1 Hz, 4H); 7.78 (m, 1H), 7.87 (d, J = 8.4 Hz, 2H); 11.80 (bs, exchangeable, 1H)

A2 (E)-3-(1-Phenylmethanesulfonyl-1H-pyrrol-3-yl)-N-(tetrahydropyran-2-yloxy)-acrylamide

0.295 g of (E)-3-(1-phenylmethansulfonyl-1H-pyrrol-3-yl)-acrylic acid (compound B1), 0.152 g of N-hydroxybenzotriazole hydrate (HOBt·H_2O) and 561 µl of triethylamine are dissolved in 20 ml of N,N-dimethylformamide (DMF) at room temperature. Afterwards it is added 0.601 g of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide hydrochloride (EDC·HCl) and stirred for 1 hour at room temperature. Then is added 0.152 g of O-(tetrahydro-2H-pyran-2-yl)-hydroxylamine and stirred for 2 hour. The DMF is evaporated under high vacuo. Water is added and the mixture was extracted with ethyl acetate. The organic phase is dried over sodium sulfate. Then it is filtered and evaporated under vacuo. The crude product is purified by silica gel flash chromatography using a gradient of dichloromethane/methanol from 99:1 to 98:2 to give 0.189 g of the title compound as a pale grey solid.

MS (ESI): 390.9 (MH^+, 100%)

^{1}H-NMR (DMSO-d6): 1.60 (m, 6H); 3.51 (m, 1H); 3.91 (m, 1H); 4.89 (m, 1H); 5.00 (s, 2H); 6,18 (d, J = 15.3 Hz, 1H); 6.50 (s, 1H); 6.96 (m, J =5.2 Hz, 1H); 7.10 (m, J_1 = 7.3 Hz, J_2 = 7.9 Hz, 2H); 7.30 (m, J_1 = 5.1 Hz, J_2 = 7.3 Hz, J_3= 8.1 Hz, J_4 = 8.1 Hz, J_5 = 15.2 Hz, 5H); 10.60 (s, exchangeable, 1H); 11.08 (bs, exchangeable, 1H)

A3 (E)-3-(1-(Biphenyl-4-sulfonyl)-1H-pyrrol-3-yl)-N-(tetrahydro-pyran-2-yloxy)-acrylamide

The method used for preparation of this compound is analogous to the method described for compound A2 with the exception that the product is purified by crystallization from water and methanol.

Starting materials: (E)-3-[1-(biphenyl-4-sulfonyl)-1H-pyrrol-3-yl]-acrylic acid (compound B2 7d) (0.300 g), HOBt·H_2O (0.130 g), triethylamine (668 µl), DMF (20 ml), EDC·HCl (0.508 g), O-(tetrahydro-2H-pyran-yl)hydroxylamine (0.089 g). Reaction conditions: room temperature, 1 hour; room temperature, 18 hours.

Yield: 0.345 g, pale grey solid

MS (ESI): 452.8 (MH^+); 369.0 (MH^+ -C_5H_9O, 100%)

^{1}H-NMR (DMSO-d6): 1.61 (m, 6); 3.50 (m, 1H); 3.92 (m, 1H); 4.87 (m, 1H); 6.21 (d, J = 14.7 Hz, 1H); 6.60 (s, 1H); 7.48 (m, J = 6.9 Hz, 5H); 7.72 (m, J_1 =7.0 Hz, J_2 = 14.7 Hz, 3H); 7.98 (d, J = 8.5 Hz, 2H); 8.06 (d, J = 8.6 Hz, 2H); 11.06 (bs, exchangeable, 1H)

A4 (E)-3-[1-(4-Dimethylamino-benzenesulfonyl)-1H-pyrrol-3-yl]-N-(tetrahydro-pyran-2-yloxy)-acrylamide

The method used for preparation of this compound is analogous to the method described for compound A2 with the exception that the product is purified by silica gel flash chromatography using a gradient of dichloromethane and methanol from 99:1 to 98:2.

Starting materials: (E)-3-[1-(4-dimethylamino-benzensulfonyl)-1H-pyrrol-3-yl)-acrylic acid (compound B3) (0.150 g), HOBt·H_2O (0.072 g), triethylamine (259 µl), DMF (10 ml), EDC·HCl (0.269 g), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.049 g). Reaction conditions: room temperature, 1 hour; room temperature, 17 hours.

Yield: 0.187 g, pale red solid

MS (ESI): 419.2 (MH^+); 336.0 (MH^+ -C_5H_9O, 100%)

^{1}H-NMR (DMSO-d6): 1.61 (m, 6);); 3.02 (s, 6H); 3.50 (m, 1H); 3.92 (m, 1H); 4.85 (m, 1H); 6.19 (m, 1H); 6.50 (m, 1H); 6.75 (m, J = 9.2 Hz, 2H); 7.31 (m, 2H); 7.64 (m, J = 9.2 Hz, 3H); 11,01 (bs, exchangeable, 1H)

A5 (2-{(E)-3-[1-(Toluene-4-sulfonyl)-1-H-pyrrol-3-yl]-allanoylamino}-phenyl)-carbamic acid *tert*-butyl ester

The method used for preparation of this compound is analogous to the method described for compound A2 with the exception that the product is purified by silica gel flash chromatography using a gradient of dichloromethane and methanol from 99:1 to 98:1.

Starting materials: (E)-3-[1-(toluene-4-sulfonyl)-1H-pyrrol-3yl]-acrylic acid (compound A1) (0.400 g), HOBt·H_2O (0.285 g), triethylamine (652 µl), DMF (25 ml), EDC·HCl (0.698 g), N-BOC-1,2,-phenylenediamine (0.286 g). Reaction conditions: room temperature, 1 hour; room temperature, 2 hours.

Yield: 0.609 g, pale grey solid

MS (ESI): 481.7 (MH^+, 100%)

^{1}H-NMR (DMSO-d6): 1.40 (m, 9H); 2.39 (s, 3H); 6.61 (m, J_1 = 1.7 Hz, J_2 = 2.2 Hz, J_3 = 5.0 Hz, 2H); 7.09 (m, J_1 = 1.8 Hz, J_2 = 2.3 Hz, 2H); 7.37 (m, J_1 = 2.0 Hz, J_2 = 5.0 Hz, J_3 = 8.0 Hz, 4H); 7.64 (m, 1H); 7.88 (d, J = 8.4 Hz, 2H); 8.41 (s, exchangeable, 1H); 9.57 (s, exchangeable, 1H)

A6 {2-[(E)-3-[1-(Phenylmethanesulfonyl-1-H-pyrrol-3-yl)-allanoylamino]-phenyl}-carbamic acid *tert*-butyl ester

The method used for preparation of this compound is analogous to the method described for compound A2 with the exception that the product is purified by silica gel flash chromatography using a gradient of dichloromethane and methanol from 99:1 to 95:5.

Starting materials: (E)-3-(1-phenylmethansulfonyl-H-pyrrol-3yl)-acrylic acid (compound B1) (0.180 g), HOBt·H_2O (0.090 g), triethylamine (295 µl), DMF (10 ml), EDC·HCl (0.315 g), N-BOC-1,2,-phenylenediamine (0.081.g). Reaction conditions: room temperature, 1 hour; room temperature, 17 hours.

Yield: 0.218 g, pale grey solid

MS (ESI): 504.0 (MNa^+, 100%); 481.8 (MH^+)

^{1}H-NMR (DMSO-d6): 1.42 (m, 9H); 5.04 (s,2H); 6.56 (m, J_1 = 2.2 Hz, J_2 = 10.2 Hz, 2H); 7.14 (m, J_1 = 2.2 Hz, J_2 = 5.5 Hz, J_3 = 10.1 Hz, 4H); 7.36 (m, J_1 = 5.5 Hz, J_2 = 7.2 Hz, 4H); 7.52 (m, J_1 = 2.2 Hz, J_2 = 7.2 Hz, 2H); 8.49 (s, exchangeable, 1H); 9.67 (s, exchangeable, 1H)

A7 (2-{(E)-3-[1-(Biphenyl-4-sulfonyl)-1H-pyrrol-3-yl]-allanoylamino}-phenyl)-carbamic acid *tert*-butyl ester

The method used for preparation of this compound is analogous to the method described for compound A2 with the exception that the product is purified by silica gel flash chromatography using a gradient of toluene/ethyl acetate from 99:1 to 9:1.

Starting materials: (E)-3-[1-(biphenyl-4-sulfonyl)-1H-pyrrol-3-yl)-acrylic acid (compound B2) (0.300 g), HOBt·H_2O (0.130 g), triethylamine (668µl), DMF (20 ml), EDC·HCl (0.508 g), N-BOC-1,2,-phenylenediamine (0.176 g). Reaction conditions: room temperature, 1 hour; room temperature, 17 hours.

Yield: 0.285 g, pale grey solid

MS (ESI): 543.8 (MH^+); 487.9 (MH^+ -C_4H_8); 336.1 (MH^+ -$C_{11}H_{14}N_2O_2$, 100%)

^{1}H-NMR (DMSO-d6): 1.47 (m, 9H); 6.50 (m, J= 5.4 Hz, 1H); 6.64 (m, J= 7.7 Hz, 2H); 7.10 (m, J_1 = 5.4 Hz, J_2 = 7.7 Hz, 3H); 7.51 (m, J_1 = J_2 = J_3 = 3.6 Hz, 5H); 7.73 (m, 2H); 7.81 (m, 1H); 7.96 (d, J = 8.6 Hz, 2H); 8.08 (d, J = 8.6 Hz, 2H); 8.41 (s, exchangeable, 1H); 8.59 (s, exchangeable, 1H)

A8 (2-{(E)-3-[1-(4-Dimethylamino-benzenesulfonyl)-1H-pyrrol-3-yl]-allanoylamino}-phenyl)-carbamic acid *tert*-butyl ester

The method used for preparation of this compound is analogous to the method described for compound A2 with the exception that the product is purified by crystallization from ethyl acetate.

Starting materials: (E)-3-[1-(4-dimethylamino-benzenesulfonyl)-1H-pyrrol-3-yl)-acrylic acid (compound B3) (0.150 g), HOBt·H_2O (0.072 g), triethylamine (259 µl), DMF (10 ml), EDC·HCl (0.269 g), N-BOC-1,2-phenylenediamine (0.049 g). Reaction conditions: room temperature, 1 hour; room temperature, 21 hours.

Yield: 0.142 g, pale red solid

MS (ESI): 510.9 (MH^+, 100%)

^{1}H-NMR (DMSO-d6): 1.42 (m, 9H); 3.00 (s, 6H); 6.51 (m, 2H) 6.79 (d, J= 9.2 Hz, 2H); 7.09 (m, J= 5.5 Hz, 2H); 7.36 (m, 2H); 7.50 (m, J = 5.5 Hz, 2H); 7.70 (m, J = 9.2 Hz, 2H); 8.41 (s, exchangeable, 1H); 9.55 (s, exchangeable, 1H)

A9 (E)-3-(1-[4-(([2-(1H-Indol-2-yl)-ethyl]-methyl-amino)-benzenesulfonyl]-1H-pyrrol-3-yl)-N-(tetrahydropyran-2-yloxy)-acrylamide

825 mg of (E)-3-(1-[4-(([2-(1H-indol-2-yl)-ethyl]-methyl-amino)-benzenesulfonyl]-1H-pyrrol-3-yl)-acrylic acid (compound B4), 165 mg of HOBt·H_2O and 1.24 ml of triethylamine are dissolved in 70 ml of DMF at room temperature. Afterwards it is added 726 mg of EDC·HCl and stirred for 1 hour. Then 140 mg of O-(tetrahydro-2H-pyran-2-yl)-hydroxylamine are added and stirred for 18 hour. The DMF is evaporated under high vacuum. Then water is added to the residue and extracted with ethyl acetate. The organic phase is dried over sodium sulfate and evaporated under vacuum. Then the mixture is evaporated and the crude product is purified by silica gel flash chromatography using a gradient of dichloromethane and methanol 98:2 – 9:1.

Yield: 289 mg, pale red solid

A10 (E)-3-[1-(4-Dimethylaminomethyl-benzenesulfonyl)-1H-pyrrol-3yl]-N-tetrahydro-pyran-2-yloxy)-acrylamide

The method used for to preparation of the title compound is analogous to the method described for compound A9.

Starting materials: (E)-3-[1-(4-Dimethylaminometyl-benzenesulfonyl)-1H-pyrrol-yl]-acrylic acid (compound B5) (1.78 g), HOBt·H_2O (366 mg), triethylamine (2.1 ml), DMF (80 ml), EDC·HCl (1.54 g), O-(tetrahydro-2H-pyran-2-yl)-hydroxylamine (306 mg). Reaction condition: room temperature, 1 hour; room temperature, 48 hours.

Yield: 835 mg, pale yellow solid

B1 (E)-3-(1-Phenylmethansulfonyl-1H-pyrrol-3-yl)-acrylic acid

The method used for preparation of this compound is analogous to the method described for compound A1 with the exception that the product is isolated by crystallization from a mixture of aceton (29.7 g), water (10.8 g) and HCl ($C_{(HCl)}$=1 mol/l, 5.3 g).

Starting materials: (E)-3-(1-phenylmethansulfonyl-1H-pyrrol-3-yl)-acrylic acid *tert*-butylester (compound C2) (1.45g), CH_2Cl_2 (80 ml), TFA (8 ml). Reaction conditions: room temperature, 2 hours.

Yield: 0.660 g, pale grey crystals

MS (TSP): 289.9($M-H^+$, 100%)

^{1}H-NMR (DMSO-d6): 5.00 (s, 2H); 6,21 (d, J= 15.9 Hz, 1H); 6.72 (m, J_1=1.9 Hz, J_2= 3.4 Hz, 1H); 7.01 (m, J= 5.3, 1H); 7.10 (m, J= 1.6 Hz, 2H); 7.31 (m, 7.41 (m, J_1= 1.6 Hz, J_2= 1.9 Hz, J_3= 3.4 Hz, J_4= 5.3 Hz, J_5= 16.1 Hz, 4H)

B2 (E)-3-[1-(Biphenyl-4-sulfonyl)-1H-pyrrol-3-yl]-acrylic acid

The method used for preparation of this compound is analogous to the method described for compound A1.

Starting materials: (E)-3-[1-(biphenyl-4-sulfonyl)-1H-pyrrol-3-yl)-acrylic acid *tert*-butyl ester (compound C3) (1.05 g), CH_2Cl_2 (100 ml), TFA (10 ml). Reaction conditions: room temperature, 21 hours.

Yield: 0.710 g, pale yellow solid

MS (ESI): 728.7 ($2MNa^+$, 100%); 354.1 (MH^+)
^{1}H-NMR (DMSO-d6): 6.29 (d, J = 16.0 Hz, 1H); 6.81 (m, J_1 = 1.2 Hz, J_2 = 1.8 Hz, J_3 = 3.0 Hz, 1H); 7.49 (m, J_1 = 3 Hz, J_2 = 7.7 Hz, J_0 = 16,0 Hz, 5H); 7.75 (m, J_1 =1.3 Hz, J_2 = 1.8 Hz, J_3 = 7.7 Hz, 2H); 7.85 (s, 1H); 7.95 (d, J = 8.6 Hz, 2H); 8.09 (d, J = 8.6 Hz, 2H); 12.17 (bs, exchangeable, 1H)

B3 (E)-3-[1-(4-Dimethylamino-benzensulfonyl)-1H-pyrrol-3-yl)-acrylic acid

The method used for preparation of this compound is analogous to the method described for compound A1.
Starting materials: (E)-3-[1-(4-dimethylamino-benzensulfonyl)-1H-pyrrol-3-yl)-acrylic acid *tert*-butyl ester (compound C4) (0.801 g), CH_2Cl_2 (100 ml), TFA (10 ml). Reaction conditions: room temperature, 16 hours.
Yield: 0.550 g, pale red solid
MS (ESI): 662.7 ($2MNa^+$, 100%); 321.0 (MH^+)
^{1}H-NMR (DMSO-d6): 2.98 (s, 6H); 6.16 (d, J = 15.8 Hz, 1H); 6.68 (m, J = 3.2 Hz, 1H); 6.75 (m, J = 9.2 Hz, 2H); 7.29 (m, J = 2.9 Hz, 1H); 7.43 (d, J = 15.9 Hz, 1H); 7.70 (m, J = 9.1 Hz, 3H); 12.11 (bs, exchangeable, 1H)

B4 (E)-3-(1-[4-(([2-(1H-Indol-2-yl)-ethyl]-methyl-amino)-benzenesulfonyl]-1H-pyrrol-3-yl)-acrylic acid

1.01 g of (E)-3-(1-[4-(([2-(1H-indol-2-yl)-ethyl]-methyl-amino)-benzenesulfonyl]-1H-pyrrol-3-yl)-acrylic acid *tert*-butyl ester (compound C5) are dissolved in 100 ml of dichloromethane and stirred for 5 minutes. It is added 10 ml of TFA and the mixture stirred for 19 hour. The solution is evaporated under vacuum. Then is added toluene to the residue (small amount to purify the TFA salt) and evaporated under vacuum.
Yield: 1.32 g, Pale brown solid

B5 (E)-3-[1-(4-Dimethylaminometyl-benzenesulfonyl)-1H-pyrrol-yl]-acrylic acid

The method used for to preparation of this compound is analogous to the method described for compound B4.
Starting materials: (E)-3-[1-(4-Dimethylaminometyl-benzenesulfonyl)-1H-pyrrol-yl]-acrylic acid *tert*-butyl ester (compound C6) (2.13 g), TFA (10 ml); 24 hour.
Yield: 3.21 g (with 3 TFA salt), pale brown solid

C1 (E)-3-[1-(Toluene-4-sulfonyl)-1H-pyrrol-3yl]-acrylic acid *tert*-butyl ester

0.230 g of sodium hydride (60%) is suspended in 6 ml of tetrahydrofurane under nitrogen at –30°C. 1.01 g of (E)-3-(1H-pyrrol-3-yl)acrylic acid *tert*-butyl ester (compound D1) are added to the suspension and warmed slowly to room temperature and stirred for 30 minutes. Afterwards it is recooled to –30°C and 1.19 g of p-toluenesulfonylchloride are added and stirred for 2.5 hours. The suspension is warmed slowly at room temperature and 40 ml of saturated aqueous sodium chloride solution are added. The mixture is extracted with ethyl acetate. The combined organic phase is dried over sodium sulfate

(Na_2SO_4). Afterwards it is filtered and evaporated under vacuo. The crude product is purified by silica gel flash chromatography using a gradient of hexane-ethyl acetate from 9:1 to 1:1 to give 1.60 g of the title compound as a pale yellow solid.

MS (ESI): 347.6 (MH^+); 291.9 (MH^+ -C_4H_9, 100%)

^{1}H-NMR (DMSO-d6): 1.43 (s, 9H); 2.37 (s, 3H); 6,21 (d, J = 15.9 Hz, 1H); 6.74 (m, J = 3.1 Hz, 1H); 7.40 (m, J_1 = 15.9 Hz, J_2 = 12.7 Hz, J_3 = 3.2 Hz, 4H); 7.82 (m, J = 12.6 Hz, 3H)

C2 (E)-3-(1-Phenylmethansulfonyl-1H-pyrrol-3-yl)-acrylic acid *tert*-butylester

The method used for preparation of this compound is analogous to the method described for compound C1 with the exception that the product is purified by silica gel flash chromatography using gradient of hexane/ethyl acetate from 8:1 to 5:1.

Starting materials: sodium hydride 60% (0.240 g), (E)-3-(1H-pyrrol-3-yl)-acrylic acid *tert*-butyl ester (compound D1 4) (1.01 g), α-toluenesulfonylchloride (1.19 g). Reaction conditions: -30°C, 30 min; -30°C, 2.5 hours.

Yield: 1.45 g, pale yellow solid

MS (TSP): 346.3 (M-H^+, 100%)

^{1}H-NMR (DMSO-d6): 1.47 (s, 9H); 5.00 (s, 2H); 6,21 (d, J = 15.8 Hz, 1H); 6.72 (m, J_1 =1.8 Hz, J_2 = 3.3 Hz, 1H); 6.98 (m, J = 5.3, 1H); 7.09 (m, J_1 = 2.1 Hz, J_2 = 7.8 Hz, 2H); 7.31 (m, J_1 = 1.9 Hz, J_2= 3.5 Hz, J_3 = 5.4 Hz, J_4 = 7.7 Hz, J_5 = 15.7 Hz, 5H)

C3 (E)-3-[1-(Biphenyl-4-sulfonyl)-1H-pyrrol-3-yl]-acrylic acid *tert*-butyl ester

The method used for preparation of this compound is analogous to the method described for compound C1 with the exception that the product is purified by silica gel flash chromatography using a gradient of petroleum ether/diethylether from 7:1 to 1:1.

Starting materials: sodium hydride 60% (0.207 g), (E)-3-(1H-pyrrol-3-yl)-acrylic acid *tert*-butyl ester (compound D1) (0.531 g), 4-biphenylsulphonylchloride (0.834 g). Reaction conditions: -30°C, 10 min; -30°C, 30 min.

Yield: 1.05 g, pale yellow solid

MS (ESI): 354.0 (MH^+ -C_4H_9, 100%)

^{1}H-NMR (DMSO-d6): 1.45 (s, 9H); 6,26 (d, J = 15.9 Hz, 1H); 6.80 (m, J = 1.7 Hz, 1H); 7.47 (m, J = 15.7 Hz, 5H); 7.72 (m, J = 1.8 Hz, 2H); 7.87 (m, 1H), 7.92 (d, J = 8.7 Hz, 2H); 8.09 (d, J = 8.6 Hz, 2H)

C4 (E)-3-[1-(4-Dimethylamino-benzensulfonyl)-1H-pyrrol-3-yl]-acrylic acid *tert*-butyl ester

The method used for preparation of this compound is analogous to the method described for compound C1 with the exception that the product is purified by silica gel flash chromatography using a gradient of petroleum ether/diethylether from 7:1 to 1:1.

Starting materials: sodium hydride 60% (0.031 g), (E)-3-(1H-pyrrol-3-yl)-acrylic acid *tert*-butyl ester (compound D1) (0.100 g), 4-dimethylamino-benzenesulfonyl chloride (0.145 g). Reaction conditions: -30°C, 45 min; -30°C, 2.5 hours.

Yield: 0.160 g, pale red solid

MS (ESI): 376.8 (MH^+); 321.0 (MH^+ -C_4H_9, 100%)
^{1}H-NMR (DMSO-d6): 1.42 (s, 9H); 3.00 (s, 6H); 6.19 (d, *J* = 15.8 Hz, 1H); 6.72 (m, *J* = 9.2 Hz, 3H); 7.25 (m, 1H); 7.37 (d, *J* = 15.8 Hz, 1H); 7.69 (m, *J* = 9.1 Hz, 3H)

C5 (E)-3-(1-[4-(([2-(1H-Indol-2-yl)-ethyl]-methyl-amino)-benzenesulfonyl]-1H-pyrrol-3-yl)-acrylic acid *tert*-butyl ester

1.50 g of (E)-3-[1-(4-bromomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylic acid *tert*-butyl ester (compound D2) are dissolved in 70 ml of ethanol at room temperature. After addition of 0.486 ml of triethylamine and 696 mg of omega-methyltryptamine it is stirred for 21 hour. Then the solution is evaporated under vacuum. The crude product is purified by silica gel flash chromatography using a gradient of hexane and ethyl acetate from 5:1 - 2:1.
Yield: 1.08 g, pale yellow solid

C6 (E)-3-[1-(4-Dimethylaminometyl-benzenesulfonyl)-1H-pyrrol-yl]-acrylic acid *tert*-butyl ester

The method used for to preparation of this compound is analogous to the method described for compound C5 with the exception that the product was crystallized in ethanol.
Starting materials: (E)-3-[1-(4-Bromomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylic acid *tert*-butyl ester (compound D2) (3.94g), ethanol (150 ml), dimethylamine (1.89 g)
Yield: 2.19 g, pale yellow solid

D1 (E)-3-(1H-Pyrrol-3-yl)-acrylic acid *tert*-butyl ester

5.29 g of sodium hydride 60% is supended in 100 ml of tetrahydrofurane under nitrogen at –30°C. 27.81 g of t*ert*-butyl diphosphono acetate are added to the suspension and warmed slowly to room temperature and stirred for 30 minutes. Afterwards the mixture is recooled at –30°C and it is added 5.24 g of 1H-pyrrol-3-carbaldehyde (compound E1) and stirred at –30°C for 30 minutes. The suspension is warmed slowly to room temperature and 200 ml of aqueous ammonia solution are added. Then it is extracted with ethyl acetate. The combined organic phase is dried over Na_2SO_4, filtered and evaporated under vacuo. The crude product is purified by silica gel flash chromatography using a gradient of n-hexane-ethyl acetate from 2:1 to 1:1 to give 9.68 g of the title compound as a pale yellow solid.
MS (EI): 193.1 (M^+); 137.1 (M^+ -C_4H_8, 100%)
^{1}H-NMR (DMSO-d6): 1.45 (s, 9H); 5.96 (d, *J* = 15.7 Hz, 1H); 6.40 (m, 1H); 6.78 (m, 1H); 7.19 (m, 1H) ; 7.47 (d, *J* = 15.7 Hz, 1H); 11.11 (bs, exchangeable, 1H)

D2 (E)-3-[1-(4-Bromomethyl-benzenesulfonyl)-1H-pyrrol-3-yl]-acrylic acid *tert*-butyl ester

4.25 g of sodium hydride (60% strength) are suspended in 300 ml of THF under nitrogen at –30°C. 9.78 g of (E)-3-(1H-pyrrol-3-yl)-acrylic acid *tert*-butyl ester (compound D1) are added to the suspension and warmed slowly to room temperature during 55 min. Afterwards it is recooled to –30°C and it is added 13.98 g of 4-(bromomethyl)-benzenesulphonylchloride and stirred for 45 min. Then it is

warmed to room temperature and stirred for 2 hour. After cooling to 0-5°C water is added. Then the mixture is extracted with ethyl acetate and the organic phase is dried over sodium sulfate. The organic phase is evaporated under vacuum. The crude product is purified by silica gel flash chromatography using a gradient of hexane and ethyl acetate from 9:1- 7:1.
Yield: 17.21 g, pale yellow solid

E1 1H-Pyrrol-3-carbaldehyde

4.70 g of dimethyl-(1H-pyrrol-3-ylmethylene)-ammonium chlorid (compound F1) are dissolved in 500 ml of 5.0% aqueous sodium hydroxide solution and stirred for 4 hours at ambient temperature. Afterwards the reaction mixture is extracted exhaustively with CH_2Cl_2. The combined organic phase is dried over Na_2SO_4. Then it is filtered and evaporated under vacuo. The crude product is purified by a silica gel flash chromatography using petroleum ether/diethylether 1:1 eluent to yield 3.01 g of the title compound as a pale yellow solid.
MS (EI):95.1 (M^+, 100%)
^{1}H-NMR (DMSO-d6): 6.42 (dd, J_1 = 1.5 Hz, J_2 = 6.5 Hz, 1H) ; 6.90 (m, 1H), 7.69 (dd, J_1 = 1.5 Hz, J_2 = 6.4 Hz, 1H) ; 9.68 (s, 1H) ; 11.59 (bs, exchangeable, 1H)

F1 Dimethyl-(1H-pyrrol-3-ylmethylene)-ammonium chlorid

10.60 g of (chloromethylene)dimethylammonium chloride and 6.25 g of N-(triisopropylsilyl)-pyrrole are suspended in 200 ml of CH_2Cl_2 under nitrogen at 0-5°C. The suspension is warmed to 60°C and stirred for 30 minutes. Afterwards the mixture is cooled to ambient temperature. The suspension is filtered and washed with diethylether to give 5.67 g of the title compound as grey solid.
MS (ESI): 123.3 (MH^+, 100%)
^{1}H-NMR (DMSO-d6): 3.55 (s, 3H) ; 3.63 (s, 3H) ; 6.82 (m, J_1 = 1.4 Hz, J_2 = 1.5Hz , J_3 = J_4 = 4.8 Hz, 1H); 7.22 (dd, J_1 = 4.7 Hz, J_2 = 4.9, 1H), 8.00 (dd, J_1 = 1.6 Hz, J_2 = 1.7 Hz, 1H) ; 8.78 (s, 1H) ; 12.94 (bs, exchangeable, 1H)

Commercial utility

The N-sulphonylpyrrole derivatives of formula I or the salts of these compounds have valuable pharmacological properties by inhibiting histone deacetylase activity and function.

"Histone deacetylase" (HDAC) means an enzyme with an activity towards the ε-acetyl group of lysine residues within a substrate protein. "HDAC substrates" are histone H2A, H2B, H3 or H4 proteins and isoforms but substrate proteins different to histones like, but not limited to, heat shock protein 90 (Hsp90), tubulin or the tumor suppressor protein p53 exist. In particular histone deacetylases catalyse the hydrolysis the ε-acetyl group of lysine residues within these substrate proteins, forming the free amino group of lysine.

"Inhibition of histone deacetylase" means inhibiting the activity and function of one or more HDAC isoenzymes, in particular isoenzymes selected from the so far known histone deacetylases, namely HDAC 1, 2, 3 and 8 (class I) and HDAC 4, 5, 6, 7, 10 (class II), HDAC 11 as well as the NAD+ dependent class III (Sir2 homologues). In some preferred embodiment this inhibition is at least about 50%, more preferable at least 75% and still more preferable above 90%. Preferably, this inhibition is specific to a specific histone deacetylase class (eg HDAC class I enzymes), a selection of isoenzymes of highest pathophysiological relevance (eg HDAC1, 2, 3 enzymes) or a single isoenzyme (eg the HDAC 1 enzyme). The term "histone deacetylase inhibitor" is used to identify a compound capable of interacting with a histone deacetylase and inhibiting its activity, in particular its enzymatic activity. In this context "head group" defines the residues within an histone deacetylase inhibitor responsible for interacting with the active site of the enzyme, eg the Zn^{2+} ion.

The inhibition of histone deacetylases is determined in biochemical assays of various formats and sources of enzymatic activity. HDAC activity is used either derived from nuclear or cellular extracts or by heterologous expression of a defined HDAC isoenzymes in E.coli, insect cells or mammalian cells. Since HDAC are active in multiprotein complexes and form homo- and heterodimeres, nuclear extracts derived from human cancer cells, for example the human cervical carcinoma cell line HeLa, are preferred. These nuclear extracts contain class I and class II enzymes, but are enriched in class 1 enzymes. The biochemical assays are well described and well known to persons skilled in the art. As substrates, histone proteins, peptides derived from histone proteins or other HDAC substrates as well as acetylated lysine mimetics are used. One preferred promiscous HDAC substrate is the tripeptide Ac-NH-GGK(Ac), coupled with the fluorophore 7-aminomethylcoumarin (AMC).

The invention further relates to the use of the compounds according to this invention for inhibiting histone deacetylase activity in cells and tissues, causing hyperacetylation of substrate proteins and as functional consequence for example the induction or repression of gene expression, induction of protein degration, cell cycle arrest, induction of differentiation and/or induction of apoptosis.

"Cellular activity" of a histone deacetylase inhibitor means any cellular effect related to histone deacetylase inhibition, in particular protein hyperacetylation, transcriptional repression and activation, induction of apoptosis, differentiation and / or cytotoxicity. The term "induction of apoptosis" and analogous terms are used to identify a compound which excecutes programmed cell death in cells contacted with that compound. "Apoptosis" is defined by complex biochemical events within the contacted cell, such as the activation of cystein specific proteinases ("caspases") and the fragmentation of chromatin. Induction of apoptosis in cells contacted with the compound might not necessarily coupled with inhibition of cell proliferation or cell differentiation. Preferably, the inhibition of proliferation, induction of differentiation and/or induction of apoptosis is specific to cells with aberrant cell growth. "Cytotoxicity" in general means arresting proliferation and/or inducing apoptotic cell death in vitro in mammalian cells, in particular human cancer cells. "Induction of differentiation" is defined as a process of cellular reprogramming leading to a reversible or irreversible cell cycle arrest in G0 and re-expression of a subset of genes typical for a certain specialized normal cell type or tissue (eg re-expression of milk fat proteins and fat in mammary carcinoma cells).

Assays for quantification of cell proliferation, apoptosis or differentiation are well known to experts and state of the art. Examples for cellular assays for the determination of hyperacetylation of HDAC substrates are given by measuring core histone acetylation using specific antibodies by Western blotting, reporter gene assays using respective responsive promoters or promoter elements (eg the p21 promotor or the sp1 site as responsive element) or finally by image analysis again using acetylation specific antibodies for core histone proteins.

The invention further relates to a method for inhibiting cellular neoplasia by adminstration of an effective amount of a compound according to this invention to a mammal, in particular a human in need of such treatment. A "neoplasia" is defined by cells displaying aberrant cell proliferation and/or survival and/or a block in differentiation. A "benign neoplasia" is described by hyperproliferation of cells, incapable of forming an aggressive, metastasizing tumor in-vivo. In contrast, a "malignant neoplasia" is described by cells with multiple cellular and biochemical abnormalities, capable of forming a systemic disease, for example forming tumor metastasis in distant organs.

The N-sulphonylpyrrole derivatives of the present invention are preferably used for the treatment of malignant neoplasia, also described as cancer, characterized by tumor cells finally metastasizing into distinct organs or tissues. Examples of malignant neoplasia treated with the N-sulphonylpyrrole derivatives of the present invention include solid and haematological tumors. Solid tumors are exemplified by tumors of the breast, bladder, bone, brain, central and peripheral nervus system, colon, endocrine glands (e.g. thyroid and adrenal cortex), esophagus, endometrium, germ cells, head and neck, kidney, liver, lung, larynx and hypopharynx, mesothelioma, ovary, pancreas, prostate, rectum, renal, small intestine, soft tissue, testis, stomach, skin, ureter, vagina and vulva. Malignant neoplasia include inherited cancers exemplified by Retinoblastoma and Wilms tumor. In addition, malignant neoplasia include primary tumors in said organs and corresponding secondary tumors in distant

organs ("tumor metastases"). Hematological tumors are exemplified by aggressive and indolent forms of leukemia and lymphoma, namely non-Hodgkins disease, chronic and acute myeloid leukemia (CML / AML), acute lymphoblastic leukemia (ALL), Hodgkins disease, multiple myeloma and T-cell lymphoma. Also included are myelodysplastic syndrome, plasma cell neoplasia, paraneoplastic syndromes, cancers of unknown primary site as well as AIDS related malignancies.
Neoplastic cell proliferation might also effect normal cell behaviour and organ function. For example the formation of new blood vessels, a process described as neovascularization, is induced by tumors or tumor metastases. N-sulphonylpyrrole derivatives as described herein will commercially applicable for treatment of pathophysiological relevant processes caused by benign or neoplastic cell proliferation, such as but not limited to neovascularization by unphysiological proliferation of vascular endothelial cells.

Drug resistance is of particular importance for the frequent failure of standard cancer therapeutics. This drug resistance is caused by various cellular and molecular mechanisms like overexpression of drug efflux pumps, mutation within the cellular target protein or fusion proteins formed by chromosomal translocations. The commercial applicability of N-sulphonylpyrrole derivatives according to the present invention is not limited to 1st line treatment of patients. In a preferred embodiment of this invention, patients with resistance to cancer chemotherapeutics or target specific anti-cancer drugs are also amenable for treatment with these compounds for e.g. 2nd or 3rd line treatment cycles. A prominent example is given by acute promyelocytic leukemia patients with the PML-RARα fusion protein, resistant to standard therapy with retinoids. These patients can be resensitized towards retinoids by treatment with HDAC inhibitory drugs like the N-sulphonylpyrrole derivatives according to the present invention.

The invention further provides to a method for treating a mammal, in particular a human, bearing a disease different to cellular neoplasia, sensitive to histone deacetylase inhibitor therapy comprising administering to said mammal a pharmacologically active and therapeutically effective and tolerable amount of a compound according to this invention. These non malignant diseases include
(i) arthropathies and osteopathological conditions such as rheumatoid arthritis, osteoarthrtis, gout, polyarthritis, psoriatic arthrtis, and systemic lupus erythematosus.
(ii) smooth muscle cell proliferation including vascular proliferative disorders, atherosclerosis and restenosis
(iii) inflammatory conditions and dermal conditions such as ulcerative colitis, Chrons disease, allergic rhinitis, allergic dermatitis, cystic fibrosis, chronic bronchitis and asthma
(iv) endometriosis, uterine fibroids, endometrial hyperplasia and benign prostate hyperplasia
(v) cardiac dysfunction
(vi) inhibiting immunosuppressive conditions like HIV infections
(vii) neuropathological disorders like Parkinson disease, Alzheimer disease or polyglutamine related disorders

(viii) pathological conditions amenable to treatment by potentiating of endogenous gene expression as well as enhancing transgene expression in gene therapy
(ix) sensitisation to radiotherapy, such as radiation therapy of solid tumors.

The present invention further includes a method for the treatment of mammals, including humans, which are suffering from one of the abovementioned conditions, illnesses, disorders or diseases. The method is characterized in that a pharmacologically active and therapeutically effective and tolerable amount of one or more of the N-sulphonylpyrrole derivatives mentioned above, or a salt of said compounds of formula I, which function by inhibiting histone deacetylases and, by modulating protein acetylation, induce various cellular effects, in particular induction or repression of gene expression, arresting cell proliferation and/or inducing apoptosis, is administered to the subject in need of such treatment.

The invention further includes a method for treating diseases and/or disorders responsive to the inhibition of histone deacetylases, particularly those diseases mentioned above, in mammals, including humans, suffering therefrom comprising administering to said mammals in need thereof a pharmacologically active and therapeutically effective and tolerable amount of one or more of the compounds according to the present invention.

The present invention further includes a therapeutic method useful to modulate protein acetylation, gene expression, cell proliferation, cell differentiation and/or apoptosis in vivo in diseases mentioned above, in particular cancer, comprising administering to a subject in need of such therapy a pharmacologically active and therapeutically effective and tolerable amount of one or more of the abovementioned N-sulphonylpyrrole derivates, or the salts of said compounds of formula I, which function by inhibiting histone deacetylases.

The present invention further provides a method for regulating endogenous or heterologous promotor activity by contacting a cell with a compound of formula I as mentioned above.

The invention further includes a method for treating diseases, particularly those diseases mentioned above, in mammals, including humans, suffering therefrom comprising administering to said mammals in need thereof a therapeutically effective and tolerable amount of one or more of the compounds according to the present invention, optionally, simultaneously, sequentially or separately with one or more further therapeutic agents, such as e.g. those mentioned below.

The invention further relates to the use of the compounds according to the present invention for the production of pharmaceutical compositions which are employed for the treatment and/or prophylaxis of the diseases, disorders, illnesses and/or conditions as mentioned herein.

The invention further relates to the use of the compounds according to the present invention for the production of pharmaceutical compositions which are employed for the treatment and/or prophylaxis of diseases and/or disorders responsive to the inhibition of histone deacetylases, particularly those diseases mentioned above.

The invention further relates to the use of the compounds according to the present invention for the production of pharmaceutical compositions having histone deacetylases inhibitory activity.

The invention further relates to the use of the compounds according to the present invention for the production of pharmaceutical compositions for inhibiting cellular neoplasia.

The invention further relates to the use of the compounds according to the present invention for the production of pharmaceutical compositions for the treatment of a disease different to a cellular neoplasia and sensitive to histone deacetylase inhibitor therapy, such as the non-malignant diseases mentioned before.

The invention further relates to the use of the compounds according to the present invention for the production of pharmaceutical compositions for inhibiting histone deacetylase activity in the treatment of diseases responsive to said inhibition or to the functional consequences thereof.

The invention further relates to a method for treating, preventing or ameliorating the diseases, disorders, illnesses and/or conditions mentioned herein in a mammal, in particular a human patient, comprising administering a pharmacologically active and therapeutically effective and tolerable amount of one or more compounds according to the present invention to said mammal in need thereof.

The invention further relates to the compounds according to this invention for use in the treatment and/or prophylaxis of diseases, especially the diseases mentioned.

The invention further relates to pharmaceutical compositions comprising one or more of the compounds according to this invention and a pharmaceutically acceptable carrier or diluent.

The invention further relates to the use of a pharmaceutical composition comprising one or more of the compounds according to this invention and a pharmaceutically acceptable carrier or diluent in the manufacture of a pharmaceutical product, such as e.g. a commercial package, for use in the treatment and/or prophylaxis of the diseases as mentioned.

Additionally, the invention relates to an article of manufacture, which comprises packaging material and a pharmaceutical agent contained within said packaging material, wherein the pharmaceutical agent is therapeutically effective for inhibiting the effects of histone deacetylases, ameliorating the

symptoms of an histone deacetylase mediated disorder, and wherein the packaging material comprises a label or package insert which indicates that the pharmaceutical agent is useful for preventing or treating histone deacetylase mediated disorders, and wherein said pharmaceutical agent comprises one or more compounds of formula I according to the invention. The packaging material, label and package insert otherwise parallel or resemble what is generally regarded as standard packaging material, labels and package inserts for pharmaceuticals having related utilities.

The pharmaceutical compositions according to this invention are prepared by processes which are known per se and familiar to the person skilled in the art. As pharmaceutical compositions, the compounds of the invention (= active compounds) are either employed as such, or preferably in combination with suitable pharmaceutical auxiliaries and/or excipients, e.g. in the form of tablets, coated tablets, capsules, caplets, suppositories, patches (e.g. as TTS), emulsions, suspensions, gels or solutions, the active compound content advantageously being between 0.1 and 95% and where, by the appropriate choice of the auxiliaries and/or excipients, a pharmaceutical administration form (e.g. a delayed release form or an enteric form) exactly suited to the active compound and/or to the desired onset of action can be achieved.

The person skilled in the art is familiar with auxiliaries, vehicles, excipients, diluents, carriers or adjuvants which are suitable for the desired pharmaceutical formulations, preparations or compositions on account of his/her expert knowledge. In addition to solvents, gel formers, ointment bases and other active compound excipients, for example antioxidants, dispersants, emulsifiers, preservatives, solubilizers, colorants, complexing agents or permeation promoters, can be used.

Depending upon the particular disease, to be treated or prevented, additional therapeutic active agents, which are normally administered to treat or prevent that disease, may optionally be coadministered with the compounds according to the present invention. As used herein, additional therapeutic agents that are normally administered to treat or prevent a particular disease are known as appropriate for the disease being treated.

In a further aspect of the present invention, the N-sulphonylpyrrole derivatives according to this invention or the salts of said compounds of formula I, which function by inhibiting histone deacetylases, may be combined with standard therapeutic agents used for treatment of the dieseases as mentioned before. In one preferred embodiment the N-sulphonylpyrrole derivatives may be combinded with one or more known chemotherapeutic and/or with target specific anti-cancer agents. Examples of known chemotherapeutic anti-cancer agents used in cancer therapy include, but not are limited to (i) alkylating/carbamylating agents such as Cyclophosphamid (Endoxan®), Ifosfamid (Holoxan®), Thiotepa (Thiotehpa Lederle®), Melphalan (Alkeran®), or chloroethylnitrosourea (BCNU); (ii) platinum derivatives like cis-platin (Platinex® BMS), oxaliplatin or carboplatin (Cabroplat® BMS); (iii) antimitotic agents / tubulin inhibitors such as vinca alkaloids (vincristine, vinblastine, vinorelbine), taxanes such as Taxol (Paclitaxel®), Taxotere (Docetaxel®) and analogs as well as new formulations

and conjugates thereof; (iv) topoisomerase inhibitors such as anthracyclines (exemplified by Doxorubicin / Adriblastin®), epipodophyllotoxines (examplified by Etoposide / Etopophos®) and camptothecin analogs (exemplified by Topotecan / Hycamtin®); (v) pyrimidine antagonists such as 5-fluorouracil (5-FU), Capecitabine (Xeloda®), Arabinosylcytosine / Cytarabin (Alexan®) or Gemcitabine (Gemzar®); (vi) purin antagonists such as 6-mercaptopurine (Puri-Nethol®), 6-thioguanine or fludarabine (Fludara®) and finally (vii) folic acid antagonists such as methotrexate (Farmitrexat®).

Examples of target specific anti-cancer drug classes used in experimental or standard cancer therapy include but are not limited to (i) kinase inhibitors such as e.g. Glivec (Imatinib®), ZD-1839 / Iressa (Gefitinib®) or OSI-774 / Tarceva (Erlotinib®); (ii) proteasome inhibitors such as PS-341 (Velcade®); (iii) heat shock protein inhibitors like 17-allylaminogeldanamycin (17-AAG); (I v) vascular targeting agents (VAT) like combretastatin A4 phosphate and anti-angiogenic drugs in general; (v) monoclonal antibodies such as Herceptin (Trastuzumab®) or MabThera / Rituxan (Rituximab®) and conjugates of monoclonal antibodies and antibody fragments; (vi) oligonucleotide based therapeutics like G-3139 / Genasense (Oblimersen®); (vii) protease inhibitors (viii) hormonal therapeutics such as anti-estrogens (e.g. Tamoxifen), anti-androgens (e.g. Flutamide or Casodex), LHRH analogs (e.g. Leuprolide, Goserelin or Triptorelin) and aromatase inhibitors.

Other known anti-cancer agents which can be used for combination therapy include bleomycin, retinoids such as all-trans retinoic acid (ATRA), DNA methyltransferase inhibitors such as the 2-deoxycytidine derivative Decitabine (Docagen®), alanosine, cytokines such as interleukin-2, interferons such as interferon α2 or interferon-γ and finally histone deacetylase inhibitors different to Sulphonylpyrrole derivatives as described in the present invention such as SAHA, valproic acid, MS-275, Depsipeptide and butyrate analogs.

As exemplary anti-cancer agents for use in combination with the compounds according to this invention in the cotherapies mentioned herein the following drugs may be mentioned, without being restricted thereto, 5 FU, actinomycin D, ABARELIX, ABCIXIMAB, ACLARUBICIN, ADAPALENE, ALEMTUZUMAB, ALTRETAMINE, AMINOGLUTETHIMIDE, AMIPRILOSE, AMRUBICIN, ANASTROZOLE, ANCITABINE, ARTEMISININ, AZATHIOPRINE, BASILIXIMAB, BENDAMUSTINE, BICALUTAMIDE, BLEOMYCIN, BROXURIDINE, BUSULFAN, CAPECITABINE, CARBOPLATIN, CARBOQUONE, CARMUSTINE, CETRORELIX, CHLORAMBUCIL, CHLORMETHINE, CISPLATIN, CLADRIBINE, CLOMIFENE, CYCLOPHOSPHAMIDE, DACARBAZINE, DACLIZUMAB, DACTINOMYCIN, DAUNORUBICIN, DESLORELIN, DEXRAZOXANE, DOCETAXEL, DOXIFLURIDINE, DOXORUBICIN, DROLOXIFENE, DROSTANOLONE, EDELFOSINE, EFLORNITHINE, EMITEFUR, EPIRUBICIN, EPITIOSTANOL, EPTAPLATIN, ERBITUX, ESTRAMUSTINE, ETOPOSIDE, EXEMESTANE, FADROZOLE, FINASTERIDE, FLOXURIDINE, FLUCYTOSINE, FLUDARABINE, FLUOROURACIL, FLUTAMIDE, FORMESTANE, FOSCARNET, FOSFESTROL, FOTEMUSTINE, FULVESTRANT, GEFITINIB, GEMCITABINE, GLIVEC,

GOSERELIN, GUSPERIMUS, HERCEPTIN, IDARUBICIN, IDOXURIDINE, IFOSFAMIDE, IMATINIB, IMPROSULFAN, INFLIXIMAB, IRINOTECAN, LANREOTIDE, LETROZOLE, LEUPRORELIN, LOBAPLATIN, LOMUSTINE, MELPHALAN, MERCAPTOPURINE, METHOTREXATE, METUREDEPA, MIBOPLATIN, MIFEPRISTONE, MILTEFOSINE, MIRIMOSTIM, MITOGUAZONE, MITOLACTOL, MITOMYCIN, MITOXANTRONE, MIZORIBINE, MOTEXAFIN, NARTOGRASTIM, NEBAZUMAB, NEDAPLATIN, NILUTAMIDE, NIMUSTINE, OCTREOTIDE, ORMELOXIFENE, OXALIPLATIN, PACLITAXEL, PALIVIZUMAB, PEGASPARGASE, PEGFILGRASTIM, PENTETREOTIDE, PENTOSTATIN, PERFOSFAMIDE, PIPOSULFAN, PIRARUBICIN, PLICAMYCIN, PREDNIMUSTINE, PROCARBAZINE, PROPAGERMANIUM, PROSPIDIUM CHLORIDE, RALTITREXED, RANIMUSTINE, RANPIRNASE, RASBURICASE, RAZOXANE, RITUXIMAB, RIFAMPICIN, RITROSULFAN, ROMURTIDE, RUBOXISTAURIN, SARGRAMOSTIM, SATRAPLATIN, SIROLIMUS, SOBUZOXANE, SPIROMUSTINE, STREPTOZOCIN, TAMOXIFEN, TASONERMIN, TEGAFUR, TEMOPORFIN, TEMOZOLOMIDE, TENIPOSIDE, TESTOLACTONE, THIOTEPA, THYMALFASIN, TIAMIPRINE, TOPOTECAN, TOREMIFENE, TRASTUZUMAB, TREOSULFAN, TRIAZIQUONE, TRIMETREXATE, TRIPTORELIN, TROFOSFAMIDE, UREDEPA, VALRUBICIN, VERTEPORFIN, VINBLASTINE, VINCRISTINE, VINDESINE, VINORELBINE and VOROZOLE.

The person skilled in the art is aware on the base of his/her expert knowledge of the total daily dosage(s) of the additional therapeutic agent(s) coadministered. Said total daily dosage(s) can vary within a wide range.

In practicing the present invention and depending on the details, characteristics or purposes of their uses mentioned above, the compounds according to the present invention may be administered in combination therapy separately, sequentially, simultaneously or chronologically staggered (e.g. as combined unit dosage forms, as separate unit dosage forms or a adjacent discrete unit dosage forms, as fixed or non-fixed combinations, or as admixtures) with one or more standard therapeutics, in particular art-known chemotherapeutic or target specific anti-cancer agents, such as those mentioned above.

Thus, a further aspect of the present invention is a combination or pharmaceutical composition comprising a first active ingredient, which is a N-sulphonylpyrrole derivative according to this invention or a salt thereof, a second active ingredient, which is an art-known standard therapeutic, in particular art-known chemotherapeutic or target specific anti-cancer agent, such as one of those mentioned above, and optionally a pharmacologically acceptable carrier, diluent and/or excipient for sequential, separate, simultaneous or chronologically staggered use in therapy in any order, e.g. to treat, prevent or ameliorate in a patient diseases responsive to HDAC inhibitor treatment, such as the diseases, disorders or illnesses mentioned, in particular cancer.

A further aspect of the present invention is a combination comprising, in non-fixed form, one or more N-sulphonylpyrrole derivatives according to this invention or the salts thereof, and one or more art-

known standard therapeutic, in particular art-known chemotherapeutic or target specific anti-cancer agents, such as those mentioned above, for sequential, separate, simultaneous or chronologically staggered use in therapy in any order, e.g. to treat, prevent or ameliorate in a patient diseases responsive to HDAC inhibitor treatment, such as the diseases, disorders or illnesses mentioned, in particular cancer. Optionally said combination comprises instructions for its use in therapy.

A further aspect of the present invention is a combined preparation, such as e.g. a kit of parts, comprising a preparation of a first active ingredient, which is a compound according to this invention and a pharmaceutically acceptable carrier or diluent; a preparation of a second active ingredient, which is an art-known therapeutic agent, in particular an anti-cancer agent, such as e.g. one of those mentioned above, and a pharmaceutically acceptable carrier or diluent; and optionally instructions for simultaneous, sequential, separate or chronologically staggered use in therapy, e.g. to treat benign and malignant neoplasia responsive to the inhibition of histone deacetylases.

A further aspect of the present invention is a kit of parts comprising a dosage unit of a first active ingredient, which is a sulphonylpyrrole derivative mentioned in above or a salt thereof, a dosage unit of a second active ingredient, which is an art-known standard therapeutic, in particular an anti-cancer agent such as e.g. one of those mentioned above, and optionally instructions for simultaneous, sequential or separate use in therapy, e.g. to treat disorders responsive to the inhibition of histone deacetylases, such as e.g. cancer.

A further aspect of the present invention is a pharmaceutical product comprising one or more compounds according to this invention, or one or more pharmaceutical compositions comprising said compounds; and one or more art-known therapeutic agents, in particular art-known anti-cancer agents, or one or more pharmaceutical compositions comprising said therapeutic agents, such as e.g. those mentioned above, for simultaneous, sequential or separate use in therapy, e.g. to treat diseases as mentioned before, in particular cancer. Optionally this pharmaceutical product comprises instructions for use in said therapy.

A further aspect of the present invention is a pharmaceutical composition as unitary dosage form comprising, in admixture, a first active ingredient, which is a N-sulphonylpyrrole derivative according to this invention or a salt thereof, a second active ingredient, which is an art-known standard therapeutic, in particular art-known chemotherapeutic or target specific anti-cancer agent, such as one of those mentioned above, and optionally a pharmacologically acceptable carrier, diluent or excipient.

A further aspect of the present invention is a commercial package comprising one or more compounds according to the present invention together with instructions for simultaneous, sequential or separate use with one or more art-known standard therapeutic, in particular anti-cancer, agents such as those mentioned above.

The pharmaceutical compositions, combinations, preparations, formulations, kits, products or packages mentioned above may also include more than one of the compounds according to this invention and/or more than one of the art-known standard therapeutics, in particular anti-cancer agents as mentioned.

Furthermore, also an aspect of the present invention is a method for treating diseases and/or disorders responsive to the inhibition of histone deacetylases, such as e.g. cancer, in combination therapy in a patient comprising administering a pharmacologically active and therapeutically effective and tolerable amount of a pharmaceutical combination, composition, formulation, preparation or kit as described above to said patient in need thereof.

A further aspect of the present invention is a method for treating cotherapeutically diseases responsive to inhibiting histone deacetylases, such as e.g. those diseases as mentioned before, in a patient in need of such treatment comprising administering separately, sequentially, simultaneously, fixed or non-fixed a pharmacologically active and therapeutically effective and tolerable amount of one or more of the compounds according to the present invention and a pharmacologically active and therapeutically effective and tolerable amount of one or more art-known therapeutic agents, in particular anti-cancer agents, such as those mentioned above, to said patient.

In addition, compounds mentioned in aspect a of the present invention can be used in the pre- or post-surgical treatment of cancer.

In further addition, compounds mentioned in aspect a of the present invention can be used in combination with radiation therapy, in particular in sensitization of cancer patients towards standard radiation therapy.

The administration of the combinations and pharmaceutical compositions according to the invention may be performed in any of the generally accepted modes of administration available in the art. Illustrative examples of suitable modes of administration include intravenous, oral, nasal, parenteral, topical, transdermal and rectal delivery. Oral and intravenous delivery are preferred.

For the treatment of dermatoses, the N-sulphonylpyrrole derivatives of the invention are in particular administered in the form of those pharmaceutical compositions which are suitable for topical application. For the production of the pharmaceutical compositions, the compounds of the invention (= active compounds) are preferably mixed with suitable pharmaceutical auxiliaries and further processed to give suitable pharmaceutical formulations. Suitable pharmaceutical formulations are, for example, powders, emulsions, suspensions, sprays, oils, ointments, fatty ointments, creams, pastes, gels or solutions.

The pharmaceutical compositions according to the invention are prepared by processes known per se. The dosage of the active compounds is carried out in the order of magnitude customary for histone deacetylases inhibitors. Topical application forms (such as ointments) for the treatment of dermatoses thus contain the active compounds in a concentration of, for example, 0.1-99%. The customary dose in the case of systemic therapy (p.o.) is between 0.3 and 30 mg/kg per day, (i. v.) is between 0.3 and 30 mg/kg/h.

Biological Investigations

Isolation of HDAC activity from HeLa cell nuclei:

HDAC activity was isolated from nuclear HeLa extracts according to a method original described by Dignam et al. (Nucl. Acids Res. 11, pp1475, 1983). Briefly, nuclei isolated from HeLa cells (CIL SA, Seneffe, Belgium) were resuspended in buffer C (20mM Hepes pH 7.9, 25% v:v glycerol, 0.42M NaCl, 1.5mM $MgCl_2$, 0.2mM EDTA, 0.5mM PefaBloc and 0.5mM DTT) and stirred for 30min on ice. After centrifugation, the supernatant was dialysed against buffer D (40mM Tris HCl pH 7.4, 100mM KCl, 0.2mM EDTA, 0.5mM DTT and 25% v:v glycerol) for 5h at 4°C. After dialysis and centrifugation, the supernatant was stored in aliquots at –80°C and used for Western blot analysis as well as the enzymatic assay as described in the following.

Fluorimetric HDAC activity assay:

The HDAC enzyme activity assay was done as described by Wegener et al. (Chem. & Biol. 10, 61-68, 2003). Briefly 40µl of a 1:100 dilution (= 0.4µl) nuclear HeLa extract (mixture of class I and II HDACs), 29 µl enzyme buffer (15mM Tris HCl pH 8.1, 0.25mM EDTA, 250mM NaCl, 10% v:v glycerol) and 1µl test compound were added to a well of a 96well microtiter plate and reaction started by addition of 30µl substrate (Ac-NH-GGK(Ac)-AMC; final concentration 25µM and final volume 100µl). After incubation for 90min at 30°C, reaction was terminated by the addition of 25µl stop solution (50mM Tris HCl pH 8, 100mM NaCl, 0.5mg/ml trypsine and 2µM TSA). After incubation at room temperature for further 40min, fluorescence was measured using a Wallac Victor 1420 multilabel counter (Ex 355nm, Em 460nm) for quantification of AMC (7-amino-4-methylcoumarin) generated by trypsine cleavage of the deacetylated peptide. For the calculation of IC_{50} values the fluorescence in wells without test compound (1% DMSO, negative control was set as 100% enzymatic activity and the fluorescence in wells with 2µM TSA (positive control) were set at 0% enzymatic activity. The corresponding IC_{50} values of the compounds for HDAC inhibitory activity were determined from the concentration-effect curves by means of non-linear regression.

The HDAC inhibitory activity expressed by IC_{50} values for selected compounds according to the present invention is shown in the following table 1, in which the numbers of the compounds correspond to the numbers of the examples.

Table 1: HDAC inhibitory activity

Compound	IC_{50} (μM)
1 2 3 4 7 8	The IC_{50} values of these listed compounds are in the range from 0.0036 to 2.74

Cellular Histone H3 hyperacetylation assay:

To assess the cellular efficacy of an histone deactylase inhibitor in vitro, an assay was set up in black clear-bottom 96-well plates and optimized for use on the Cellomics "ArrayScan II" platform for a quantitative calculation of histone acetylation. The protocol uses a polyclonal rabbit antibody, specifically binding to acetylated lysine 23 of human histone H3 on fixed cells with an Alexa Fluor 488 labeled goat anti rabbit-IgG used for counterstaining (Braunger et al. AACR annual conference 2003, Abstract 4556).

$5x10^3$ HeLa cervical carcinoma cells/well (ATCC CCL-2) in 200μl Dulbecco's modified Eagle's medium (DMEM) containing 10% fetal calf serum were seeded at day 1 in Packard view plates and incubated for 24h under standard cell culture conditions. On day 2, 2μl test compound (100x final concentration) was added and incubation continued for further 24h. On day 3, the culture medium was discarded and attached cells fixed for 15min at room temperature by addition of 100μl fixation buffer (3.7% v:v formaldehyde in phosphate buffered saline / PBS). After discarding the fixation buffer and one wash with PBS, cells were permeabilized at room temperature by addition of 100μl/well permeabilization buffer (30,8 mM NaCl, 0,54 mM Na_2HPO_4, 0,31 mM KH_2PO_4, 5% v:v Triton X-100) for 15min at room temperature. After discarding the permeabilization buffer and addition of 100μl/well blocking solution (PBS with 0.05% v:v Tween 20 and 5% w:v milk powder) for 30min at room temperature, the 1st antibody (anti-K23 histone H3 antibody, Cell Signaling No. 9674) in blocking solution (50μl/well) was added. After incubation for 1h at 37°C, the wells were washed 5 times for 5min at room temperature with wash buffer (PBS with 0.05% v:v Tween 20) before additon of the 2nd antibody (goat-anti-rabbit Alexa Fluor 488; MoBiTec No. A-11008) in blocking solution (50μl/ well). After further incubation for 30min at 37°C, wells were washed 5 times for 5min at RT with 100μl wash buffer at room temperature. Finally, 100μl/well PBS were added and image analysis performed on the Cellomics "ArrayScan II" platform. For calculation of IC_{50} values, the nuclear fluorescence in cells

treated with and without SAHA as a reference HDAC inhibitor were taken as a positive and negative control. For IC_{50} determination, the percentage of positive cells was determined and IC_{50} calculation done from concentration-effect curves by means of non-linear regression.

The histone acetylating cellular potency expressed by EC_{50} values for selected compounds according to the present invention is shown in the following table 2, in which the numbers of the compounds correspond to the numbers of the examples.

Table 2:

Compound	EC_{50} (µM)
1 2 3 4 7 8	The EC_{50} values of these listed compounds are in the range from 2.15 to 51.3

Cellular cytotoxicity assay:

The anti-proliferative activity of the histone deacetylase inhibitory compounds as described herein, was evaluated with the HeLa cervical carcinoma cell line (ATCC CCL2) using the Alamar Blue (Resazurin) cell viability assay (O´Brien et al. Eur J Biochem 267, 5421-5426, 2000). Resazurin is reduced to the fluorescent resorufin by cellular dehydrogenase activity, correlating with viable, proliferating cells. Test compounds were dissolved as 10 mM solutions in dimethylsulfoxide (DMSO) and subsequently diluted in semi-logarithmic steps. HeLa cells were seeded into 96 well flat bottom plates at a density of 3000 cells per well in a volume of 200 µl per well. 24 hours after seeding 1 µl each of the compound dilutions were added into each well of the 96 Well plate. Each compound dilution was tested as quadruplicates. Wells containing untreated control cells were filled with 200 µl DMEM medium containing 0.5% v:v DMSO. The cells were then incubated with the substances for 48 hours at 37°C in a humidified athmosphere containing 5% carbon dioxide. To determine the viability of the cells, 20 µl of an Resazurin solution (Sigma; 90mg / l) were added. After 4 hours incubation at 37°C the fluorescence was measured at an extinction of 544 nm and an emission of 590 nm. For the calculation of the cell viability the emission value from untreated cells was set as 100% viability and the emission rates of treated cells were set in relation to the values of untreated cells. Viabilities were expressed as % values. The corresponding IC_{50} values of the compounds for cytotoxic activity are determined from the concentration-effect curves by means of non-linear regression.

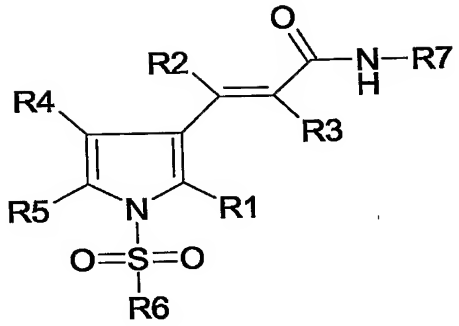
The anti-proliferative / cytotoxic potency expressed by IC_{50} values for selected compounds according to the present invention is shown in the following table 3, in which the numbers of the compounds correspond to the numbers of the examples.

Table 3:

Compound	IC_{50} (µM)
1 2 3 4 7 8	The IC_{50} values of these listed compounds are in the range from 0.8 to 21.6

Patent Claims

1. Compounds of formula I



(I)

in which

R1 is hydrogen, 1-4C-alkyl, halogen, or 1-4C-alkoxy,

R2 is hydrogen or 1-4C-alkyl,

R3 is hydrogen or 1-4C-alkyl,

R4 is hydrogen, 1-4C-alkyl, halogen, or 1-4C-alkoxy,

R5 is hydrogen, 1-4C-alkyl, halogen, or 1-4C-alkoxy,

R6 is -T1-Q1, in which

T1 is a bond, or 1-4C-alkylene,

Q1 is Ar1, Aa1, Hh1, or Ah1, in which

Ar1 is phenyl, or R61- and/or R62-substituted phenyl, in which

R61 is 1-4C-alkyl, or -T2-N(R611)R612, in which

T2 is a bond, 1-4C-alkylene, or 2-4C-alkylene interrupted by oxygen,

R611 is hydrogen, 1-4C-alkyl, hydroxy-2-4C-alkyl, 1-4C-alkoxy-2-4C-alkyl, phenyl-1-4C-alkyl, or Har1-1-4C-alkyl, in which

Har1 is optionally substituted by R6111 and/or R6112, and is a monocyclic or fused bicyclic 5- to 10-membered unsaturated heteroaromatic ring comprising one to three heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and sulfur, in which

R6111 is halogen, or 1-4C-alkyl,

R6112 is 1-4C-alkyl,

R612 is hydrogen, 1-4C-alkyl, 1-4C-alkoxy-2-4C-alkyl or hydroxy-2-4C-alkyl,

R62 is 1-4C-alkyl, 1-4C-alkoxy, halogen, cyano, 1-4C-alkoxy-1-4C-alkyl, 1-4C-alkylcarbonylamino, or 1-4C-alkylsulphonylamino,

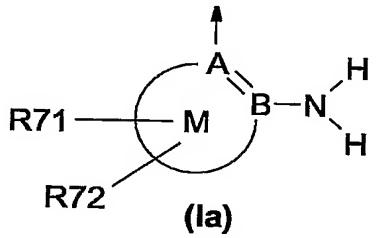
Aa1 is a bisaryl radical made up of two aryl groups,
which are selected independently from a group consisting of phenyl and naphthyl, and
which are linked together via a single bond,

Hh1 is a bisheteroaryl radical made up of two heteroaryl groups,
which are selected independently from a group consisting of monocyclic 5- or 6-membered heteroaryl radicals comprising one or two heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and sulfur, and
which are linked together via a single bond,

Ah1 is a heteroaryl-aryl radical or an aryl-heteroaryl radical made up of a heteroaryl group selected from a group consisting of monocyclic 5- or 6-membered heteroaryl radicals comprising one or two heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and sulfur, and an aryl group selected from a group consisting of phenyl and naphthyl, whereby said heteroaryl and aryl groups are linked together via a single bond,

R7 is hydroxyl, or Cyc1, in which

Cyc1 is a ring system of formula Ia



(Ia)

in which

A is C (carbon),

B is C (carbon),

R71 is hydrogen, halogen, 1-4C-alkyl, or 1-4C-alkoxy,

R72 is hydrogen, halogen, 1-4C-alkyl, or 1-4C-alkoxy,

M with inclusion of A and B is either a ring Ar2 or a ring Har2, in which

Ar2 is a benzene ring,

Har2 is a monocyclic 5- or 6-membered unsaturated heteroaromatic ring comprising one to three heteroatoms, each of which is selected from the group consisting of nitrogen, oxygen and sulfur,

and the salts of these compounds.

2. Compounds of formula I according to claim 1

in which

R1 is hydrogen, or 1-4C-alkyl,

R2 is hydrogen, or 1-4C-alkyl,

R3 is hydrogen, or 1-4C-alkyl,
R4 is hydrogen, or 1-4C-alkyl,
R5 is hydrogen, or 1-4C-alkyl,
R6 is -T1-Q1, in which
T1 is a bond, or 1-4C-alkylene,
Q1 is Ar1, or Aa1, in which
Ar1 is phenyl, or R61-substituted phenyl, in which
R61 is 1-4C-alkyl, or -T2-N(R611)R612, in which
T2 is a bond, or 1-4C-alkylene,
R611 is hydrogen, 1-4C-alkyl, or Har1-1-4C-alkyl, in which
Har1 is imidazolyl, benzimidazolyl, indolyl or pyrrolyl,
R612 is hydrogen, or 1-4C-alkyl,
Aa1 is a biphenyl radical,
R7 is hydroxyl, or 2-aminophenyl,
and the salts of these compounds.

3. Compounds of formula I according to any of the preceding claims in which
R1 is hydrogen,
R2 is hydrogen,
R3 is hydrogen,
R4 is hydrogen,
R5 is hydrogen,
R6 is -T1-Q1, or biphenyl, in which
T1 is a bond, or 1-2C-alkylene,
Q1 is Ar1, in which
Ar1 is phenyl, or R61-substituted phenyl, in which
R61 is 1-4C-alkyl, or -T2-N(R611)R612, in which
T2 is a bond, or 1-2C-alkylene,
R611 is 1-4C-alkyl, or Har1-1-2C-alkyl, in which
Har1 is benzimidazolyl, or indolyl,
R612 is 1-4C-alkyl,
R7 is hydroxyl, or 2-aminophenyl,
and the salts of these compounds.

4. Compounds of formula I according to any of the preceding claims in which
R1 is hydrogen,
R2 is hydrogen,
R3 is hydrogen,

R4 is hydrogen,
R5 is hydrogen,
R6 is -T1-Q1, biphenyl, or benzyl, in which
T1 is a bond,
Q1 is Ar1, in which
Ar1 is R61-substituted phenyl, in which
R61 is methyl, dimethylamino, or -T2-N(R611)R612, in which
T2 is methylene,
R611 is methyl, or 2-(indol-2-yl)ethyl,
R612 is methyl,
R7 is hydroxyl, or 2-aminophenyl,
and the salts of these compounds.

5. Compounds of formula I as claimed in claim 1 for use in the treatment of diseases.

6. A pharmaceutical composition comprising on or more compounds of formula I as claimed in claim 1 together with customary pharmaceutical excipients and/or vehicles.

7. Use of compounds of formula I as claimed in claim 1 for the manufacture of pharmaceutical compositions for treating diseases responsive to inhibition of histone deacetylase activity.

8. Use of compounds of formula I as claimed in claim 1 for the manufacture of pharmaceutical compositions for treating benign and/or malignant neoplasia, such as e.g. cancer.

9. Use of compounds of formula I as claimed in claim 1 for the manufacture of pharmaceutical compositions for treating diseases different to benign or malignant neoplasia, such as e.g. systemic lupus erythematosus, rheumatoid arthritis, Huntington's disease or inflammatory diseases.

10. A method for treating diseases in a patient comprising administering to said patient a therapeutically effective and tolerable amount of a compound of formula I as claimed in claim 1.

11. A method for treating benign and/or malignant neoplasia, such as e.g. cancer, in a patient comprising administering to said patient a therapeutically effective and tolerable amount of a compound of formula I as claimed in claim 1, optionally, simultaneously, sequentially or separately with one or more further therapeutic agents.

12. A method for treating non-malignant diseases, such as e.g. systemic lupus erythematosus, rheumatoid arthritis, Huntington's disease or inflammatory diseases, in a patient comprising administering to said patient a therapeutically effective and tolerable amount of a compound of

formula I as claimed in claim 1, optionally, simultaneously, sequentially or separately with one or more further therapeutic agents.

Abstract

Compounds of a certain formula I, in which R1, R2, R3, R4, R5, R6 and R7 have the meanings indicated in the description, are novel effective HDAC inhibitors.